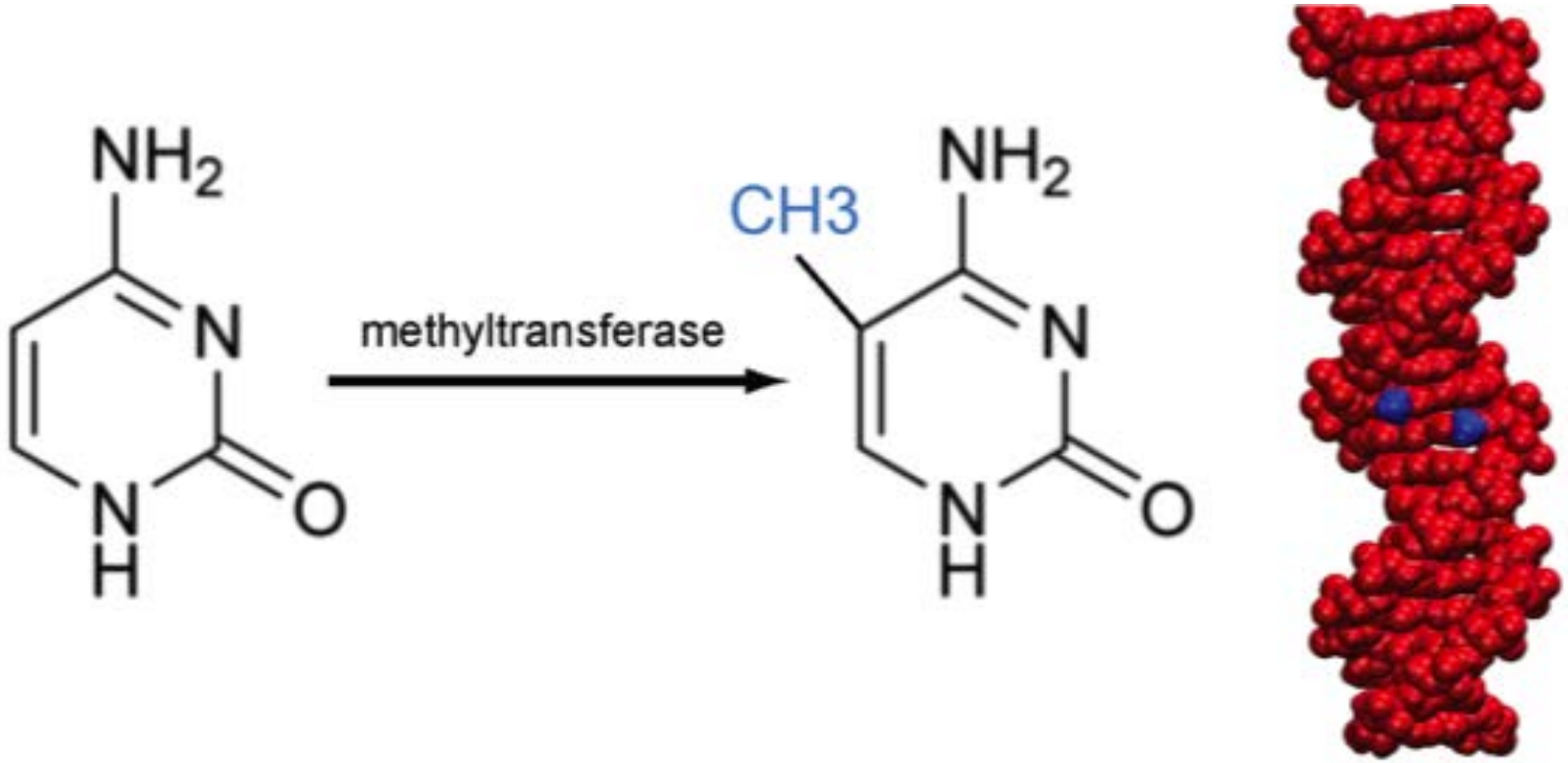
Uses and misuses of DNA Methylation to explain health inequalities

Center for Health Equity Seminar
University of California, San Francisco
December 4, 2019

David Rehkopf
Stanford University School of Medicine

Part 1: What is it?



5-methylcytosine

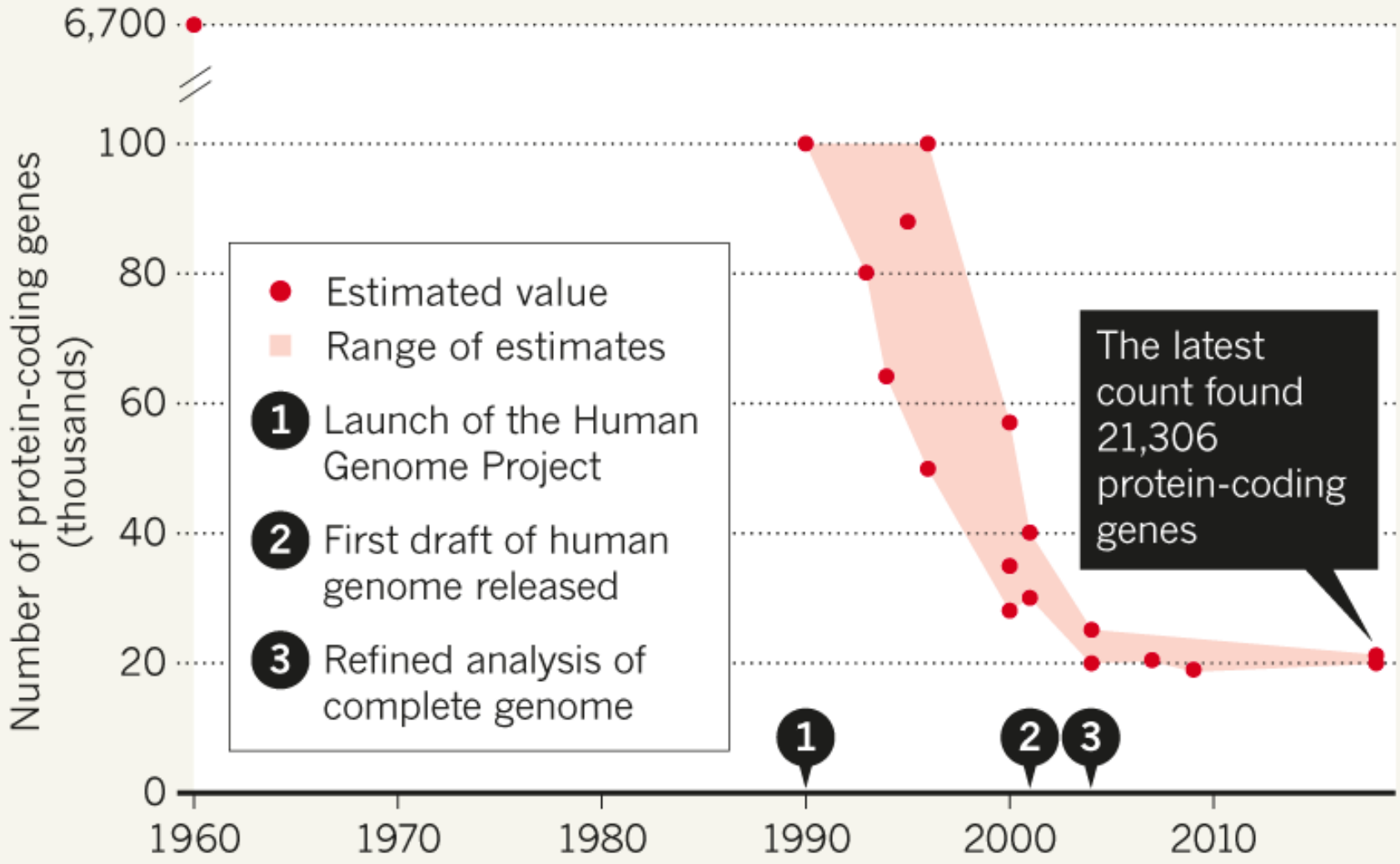
Methylation and the human genome

3,234,000,000 base pairs

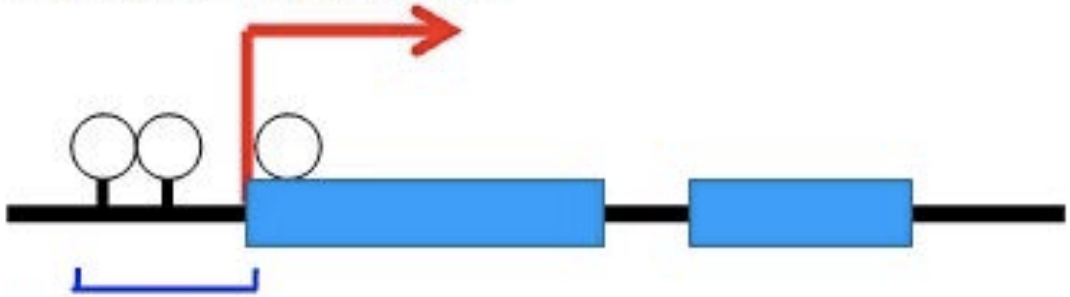
CpG 28,000,000

GENE TALLY

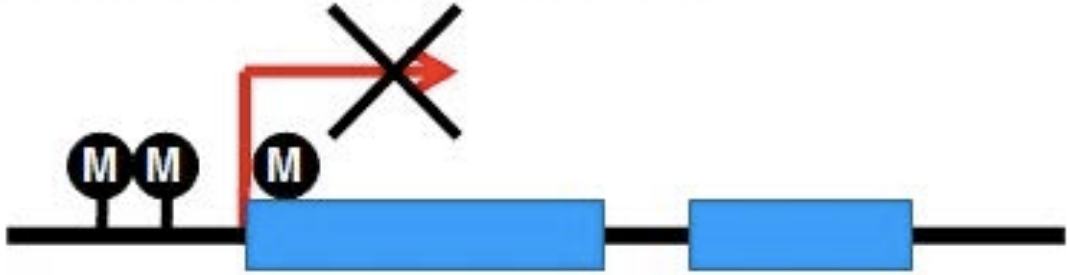
Scientists still don't agree on how many protein-making genes the human genome holds, but the range of their estimates has narrowed in recent years.

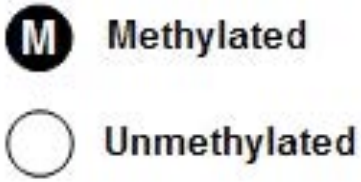


Genes that can be expressed

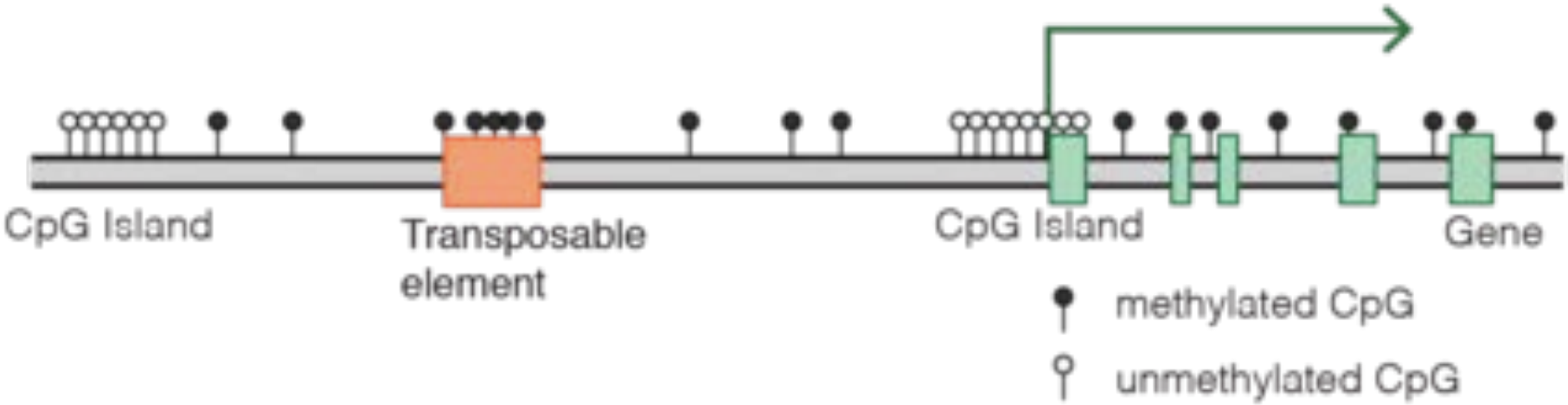


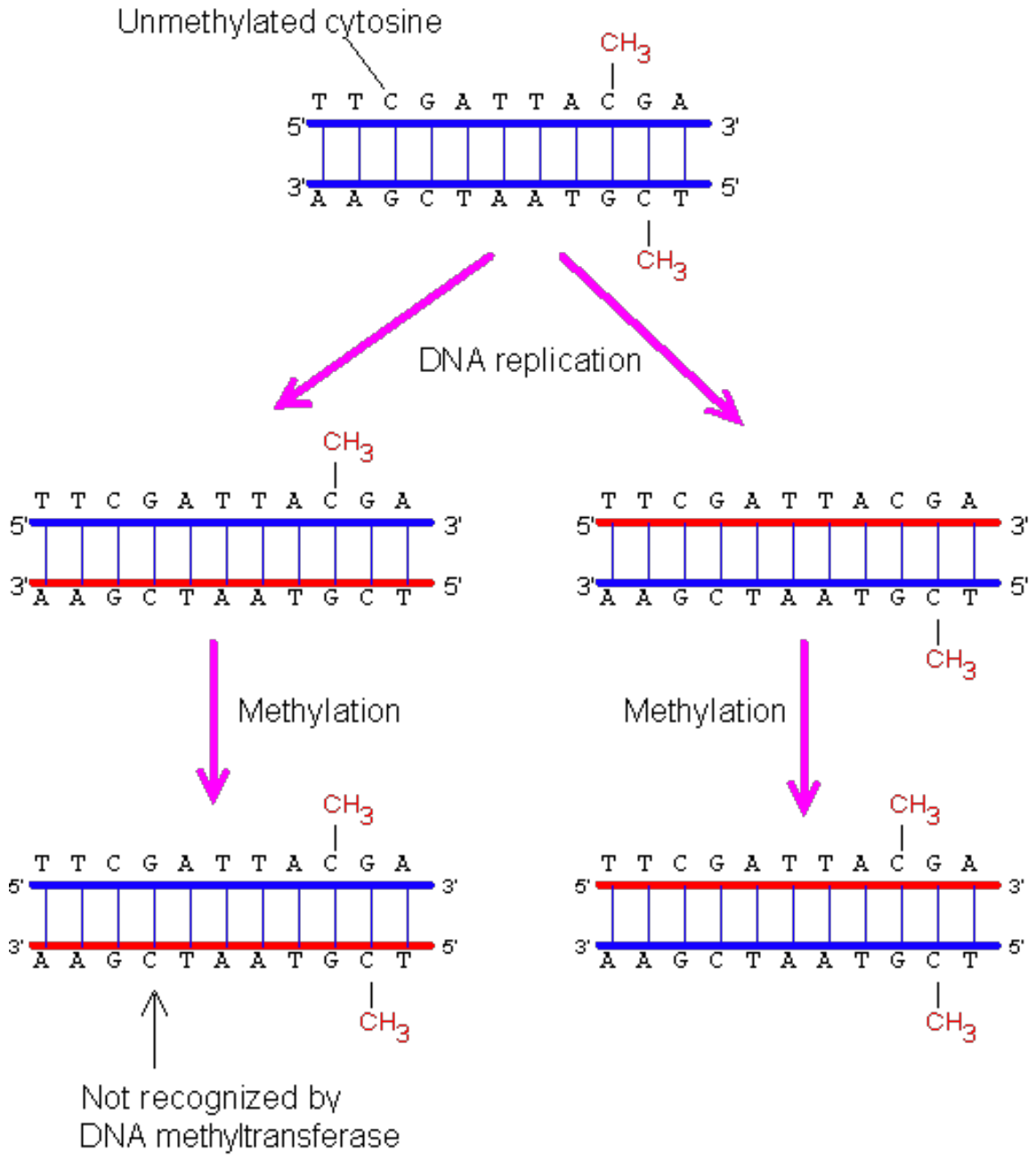
Genes inactivated by DNA methylation





Typical mammalian DNA methylation landscape




Unmethylated cytosine
CH3
T T C G A T T A C G A
5'
3'
3'
A A G C T A A T G C T
5'
CH3
DNA replication
CH3
T T C G A T T A C G A
5'
3'
3'
A A G C T A A T G C T
5'
T T C G A T T A C G A
5'
3'
3'
A A G C T A A T G C T
5'
CH3
Methylation
Methylation
CH3
T T C G A T T A C G A
5'
3'
3'
A A G C T A A T G C T
5'
CH3
CH3
T T C G A T T A C G A
5'
3'
3'
A A G C T A A T G C T
5'
CH3
Not recognized by
DNA methyltransferase

Illumina EPIC array

850,000 CpGs

In population based studies…

~100ng of DNA

~$350

SCIENTIFIC REPORTS

1. Genotype

OPEN

Identification of 55,000 Replicated DNA Methylation QTL

Allan F. McRae[1,2], Riccardo E. Marioni[3,4], Sonia Shah[1], Jian Yang[1,2], Joseph E. Powell[1], Sarah E. Harris[3,4], Jude Gibson[5], Anjali K. Henders[1], Lisa Bowdler[6], Jodie N. Painter[6], Lee Murphy[5], Nicholas G. Martin[6], John M. Starr[4,7], Naomi R. Wray[1,2], Ian J. Deary[4,8], Peter M. Visscher[1,2,4] & Grant W. Montgomery[1]

ed: 14 April 2016
ed: 12 November 2018
ied online: 04 December 2018

DNA methylation plays an important role in the regulation of transcription. Genetic control of DNA methylation is a potential candidate for explaining the many identified SNP associations with disease that are not found in coding regions. We replicated 52,916 *cis* and 2,025 *trans* DNA methylation quantitative trait loci (mQTL) using methylation from whole blood measured on Illumina HumanMethylation450 arrays in the Brisbane Systems Genetics Study (n = 614 from 177 families) and the Lothian Birth Cohorts of 1921 and 1936 (combined n = 1366). The *trans* mQTL SNPs were found to be over-represented in 1 Mbp subtelomeric regions, and on chromosomes 16 and 19. There was a significant increase in *trans* mQTL DNA methylation sites in upstream and 5′ UTR regions. The genetic

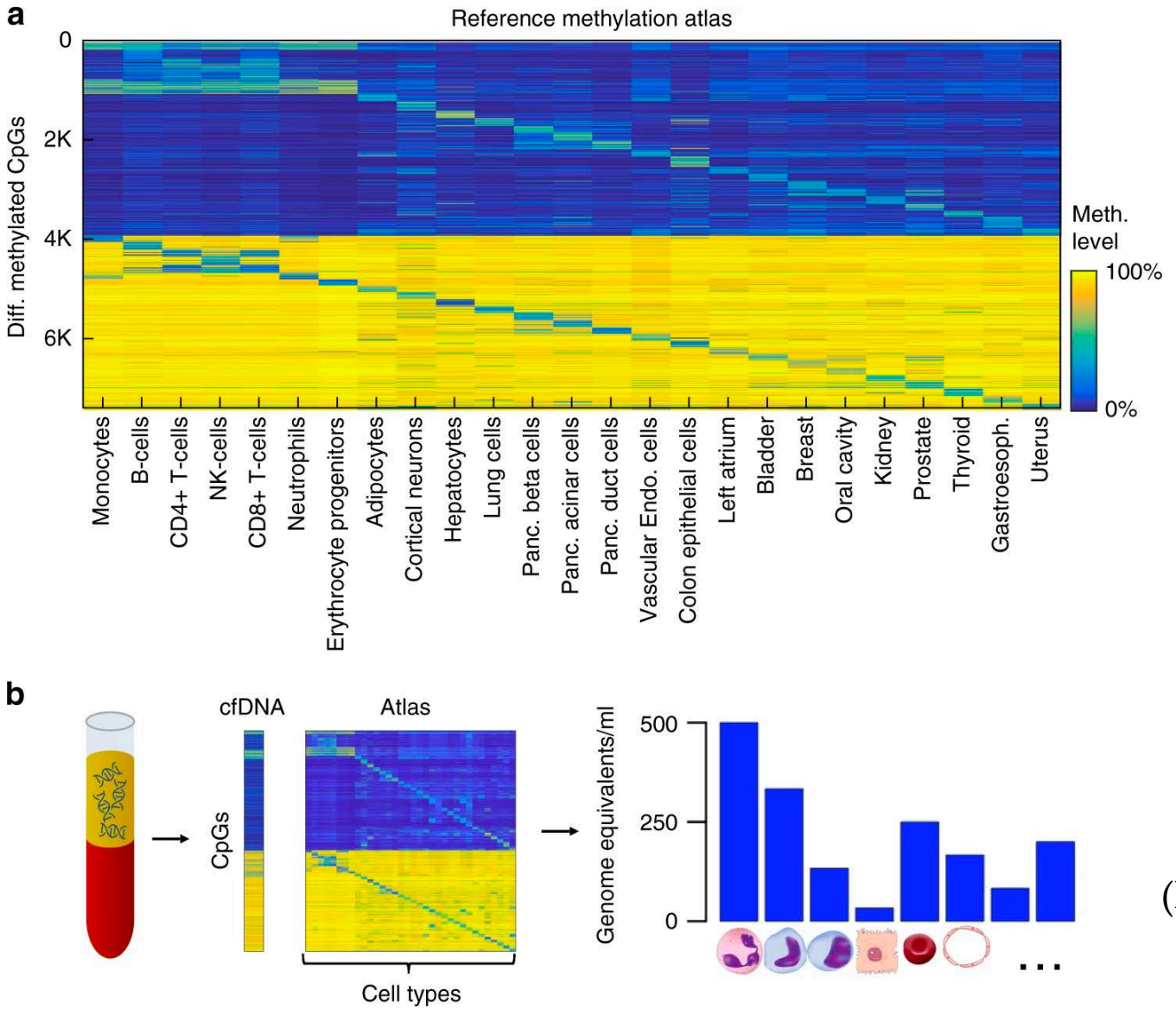
Systematic Mendelian randomization framework elucidates hundreds of genetic loci which may influence disease through changes in DNA methylation levels

Tom G. Richardson[1*], Philip C. Haycock[1], Jie Zheng[1], Nicholas J. Timpson[1], Tom R. Gaunt[1], George Davey Smith[1], Caroline L. Relton[1], Gibran Hemani[1]

[1] *MRC Integrative Epidemiology Unit (IEU), Bristol Medical School (Population Health Sciences), University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN, United Kingdom*

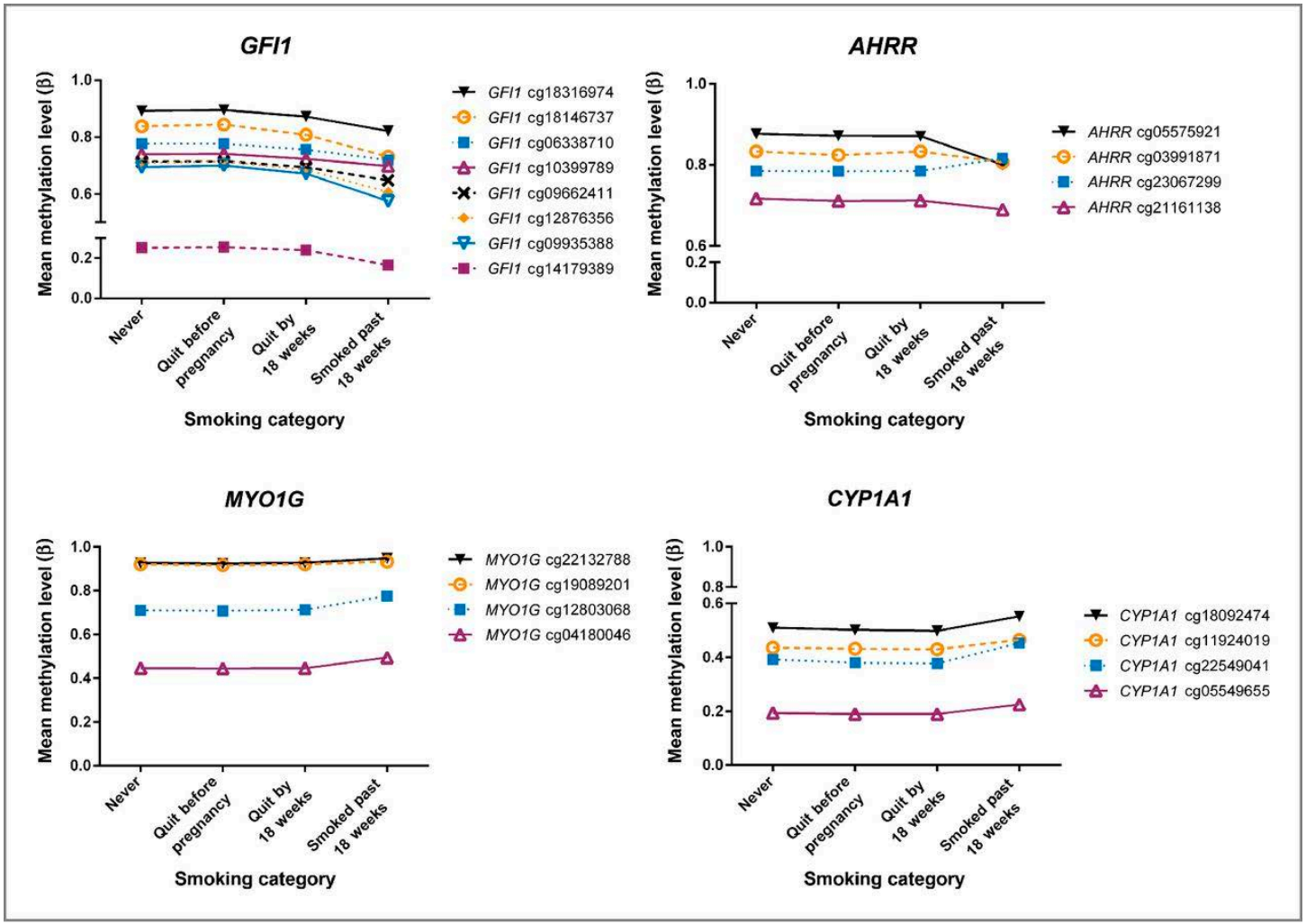
*Corresponding author: Dr. Tom G. Richardson, MRC Integrative Epidemiology Unit, Bristol Medical School (Population Health Sciences), University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK. Tel: +44 (0)117 3313370; E-mail: Tom.G.Richardson@bristol.ac.uk

2. Cell type



(Moss et al., Nature Communications, 2019)

3. Smoking / secondhand smoke



(Joubert et al., CEBP, 2014)

4. Physical toxins

ANNUAL REVIEWS

Annual Review of Public Health

Environmental Influences on the Epigenome: Exposure-Associated DNA Methylation in Human Populations

Elizabeth M. Martin and Rebecca C. Fry

Department of Environmental Sciences and Engineering, and Curriculum in Toxicology,

Table 1 Summary of exposures assessed within this review

Exposures	Global methylation	Gene-specific methylation	Exposure-associated health impact	Relevant citations
Aflatoxin B1	Hypomethylation associated with exposure	71 CpG sites associated with prenatal exposure	Hepatocellular carcinomas, reduced growth, immune deficiencies	73, 75, 185, 197
Air pollution	Hypomethylation typically associated with exposure in adults, prenatal exposure is associated with both hypo- and hypermethylation	*MAPK* pathway members, *ACE*, *iNOS*, *ICAM-1*, *TLR2*, *IL-6*, *TET1*	Accelerated lung aging, loss of lung capacity, asthma, bronchitis, emphysema, and cancer	19, 20, 28, 31, 32, 36, 39, 44, 45, 63, 69, 79, 87, 88, 98, 112, 120, 165, 168, 183
Arsenic	Hypomethylation associated with exposure with sex-specific directionality shown as well	*KCNQ1*, *SQSTM1*, sex-specific profiles	Cancer lung conditions and diabetes in adults; prenatal exposure is associated with increased incidence of infection, neurocognitive effects, and increased neonatal mortality	2, 6, 9, 13, 15, 29, 33, 34, 47, 50, 54, 65, 76, 77, 84, 97, 105, 110, 121, 136, 137, 151–153, 155, 159, 177, 184, 199
Bisphenol A	Hypomethylation associated with exposure in females, potential nonmonotonic dose responses	*SNORD*, *SULT2A1*, *COMT*	Neurocognitive effects, increased incidence of cancer, and heart conditions from prenatal exposure	52, 53, 70, 99, 133, 134
Cadmium	Hypomethylation associated with exposure	*DNMT1*	Cancer, lung, bone, and kidney disease, developmental toxicity	51, 70, 78, 103, 129, 169, 170, 187, 188

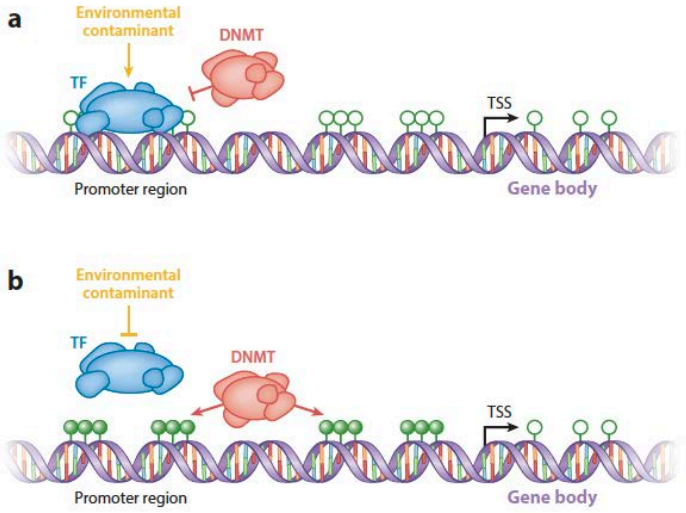
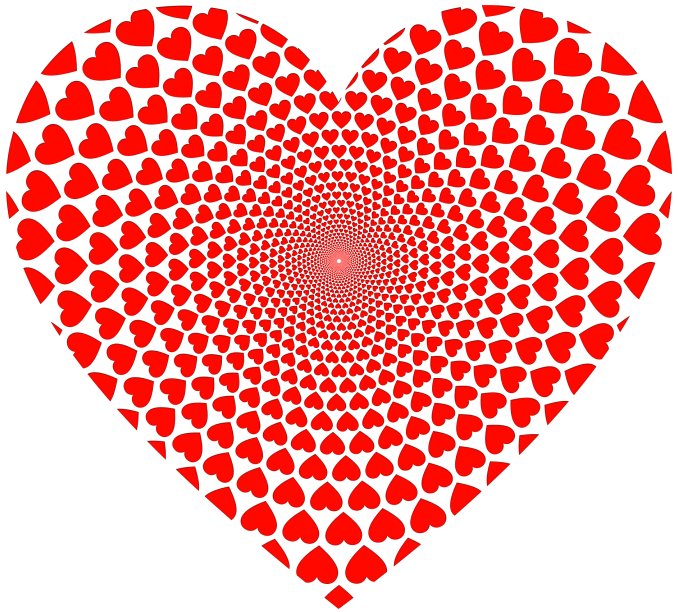


Figure 2

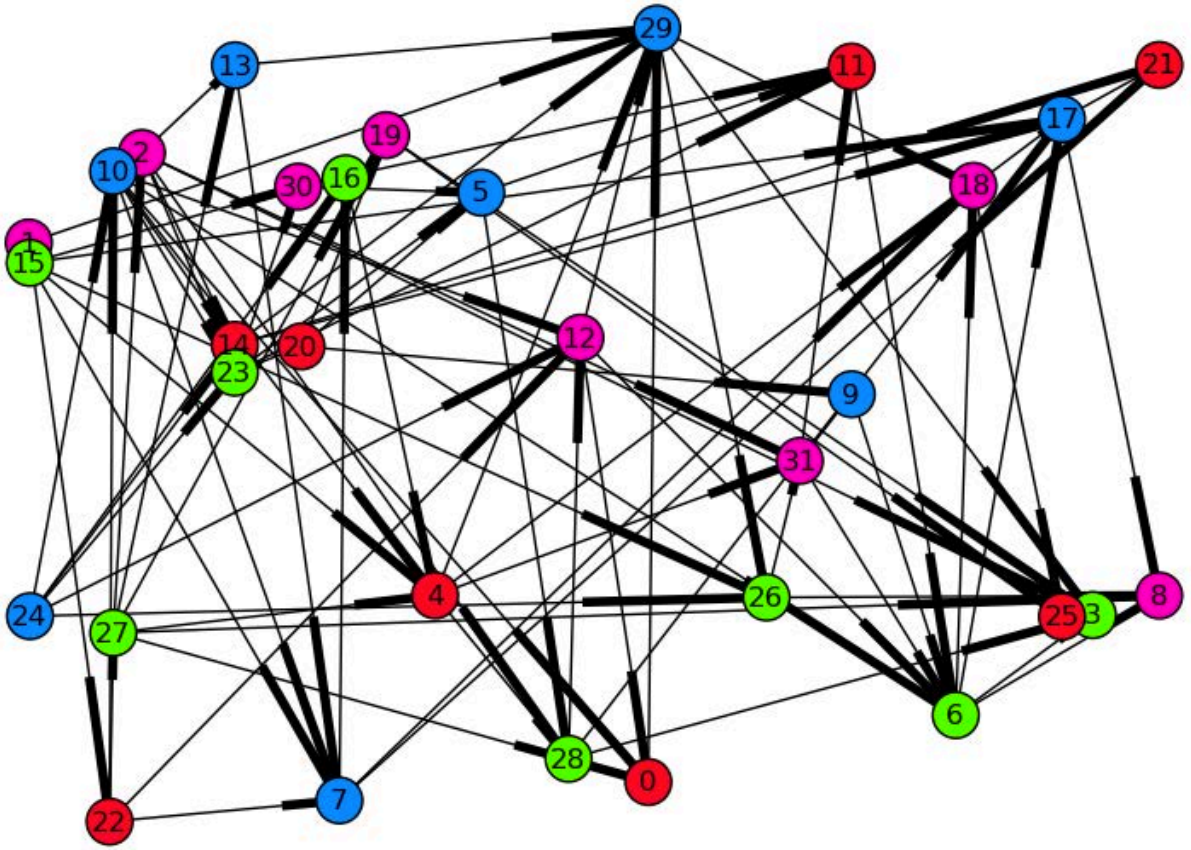
Diagram of the transcription factor occupancy theory. This hypothesis posits that presence or absence of

Part 2: Why do social scientists love it?



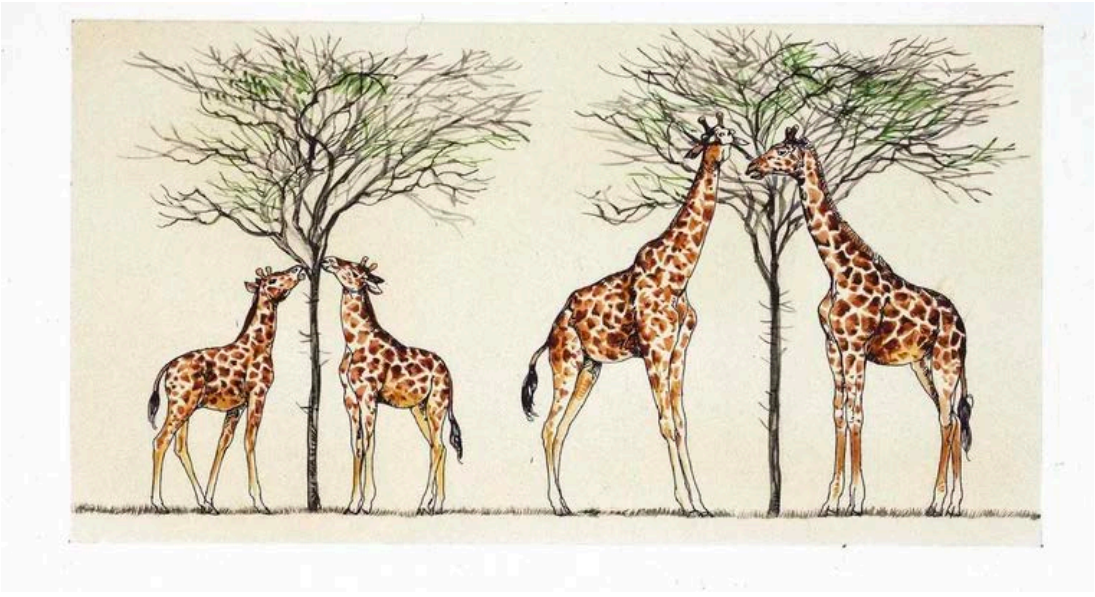
Reason 1: Biological plausibility for the effects of the social environment

Causal inference is hard



Reason 2: Objective measure of social exposures

Reason 3: Transgenerational inheritance



Reason 3: Transgenerational inheritance

Social Science & Medicine 230 (2019) 74–82

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journal homepage: www.elsevier.com/locate/socscimed

Biological pathways for historical trauma to affect health: A conceptual model focusing on epigenetic modifications

Andie Kealohi Sato Conching, Zaneta Thayer*

406A Silsby, Dartmouth College, Hanover, NH, 03755, United States

ARTICLE INFO

ABSTRACT

epigenetic modifications that can contribute to the development of poor health. The second pathway posits that poor health can occur through intergenerational epigenetic modifications in response to parental and grandparental trauma or stressor exposures. Taken together, these pathways can provide insight into the higher rates

Reason 3: Transgenerational inheritance

nature COMMUNICATIONS

COMMENT

DOI: 10.1038/s41467-018-05445-5 OPEN

A critical view on transgenerational epigenetic inheritance in humans

Bernhard Horsthemke[1]

Transgenerational epigenetic inheritance refers to the transmission of epigenetic information through the germline. While it has been observed in plants, nematodes and fruit flies, its occurrence in mammals—and humans in particular—is the matter of controversial debate, mostly because the study of transgenerational epigenetic inheritance is confounded by

FOUR DECADES OF EXCITING BIOLOGY 40 SINCE 1974 Leading Edge Review

Cell

Transgenerational Epigenetic Inheritance: Myths and Mechanisms

Edith Heard[1,2,*] and Robert A. Martienssen[3,4,*]
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[2]Collège de France, 11 place Marcelin-Berthelot, Paris 75005, France
[3]Howard Hughes Medical Institute and Gordon and Betty Moore Foundation, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA
[4]Chaire Blaise Pascal, IBENS, École Normale Supérieure, Paris 75230, France
*Correspondence: edith.heard@curie.fr (E.H.), martiens@cshl.edu (R.A.M.)
http://dx.doi.org/10.1016/j.cell.2014.02.045

Since the human genome was sequenced, the term "epigenetics" is increasingly being associated with the hope that we are more than just the sum of our genes. Might what we eat, the air we breathe, or even the emotions we feel influence not only our genes but those of descendants? The environment can certainly influence gene expression and can lead to disease, but transgenerational consequences are another matter. Although the inheritance of epigenetic characters can certainly occur—particularly in plants—how much is due to the environment and the extent to which it happens in humans remain unclear.

Why do social scientists love DNAm?

Reason 1: Biological plausibility for the effects of the social environment

~~Reason 2: Objective measure of social exposures~~

~~Reason 3: Transgenerational inheritance~~

Part 3: Why do social scientists hate it?

Reason 1. Biological measures distract from caring about social causes

Stormy Weather: *Race*, Gene Expression, and the Science of Health Disparities

Nancy Krieger, PhD

In the current US political climate, conservative foundations are seeking to frame debates over determinants of racial/ethnic health dis-

ONE WORD APTLY DESCRIBES the state of contemporary dis-

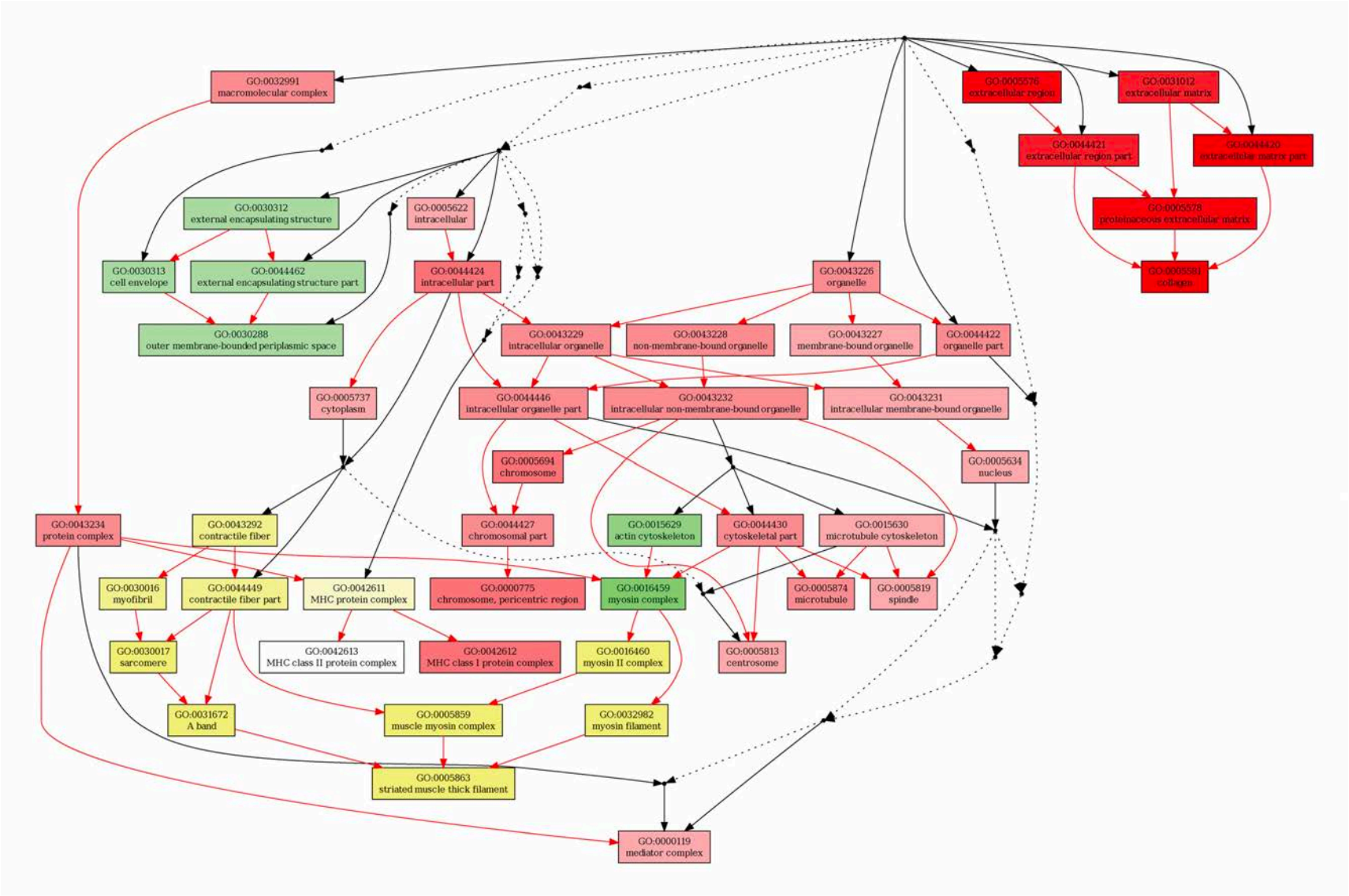
The notion, however, that scientific thinking and work must

best.[22,23,91] Indeed, evidence obtained from the National Institutes of Health (NIH) CRISP database[93] (a public access database providing information on all NIH grants awarded since 1975) suggests that researchers with an interest in genetics are unlikely to have their share of the NIH budget seriously encroached on by researchers with an interest in the impact of racial inequality on health. For the decade 1995 to 2004, use of the search term *genetics* in CRISP identified 21 956 new grants (including 181 additionally indexed by the term *race*). By contrast, only 44 new grants were indexed by the terms *racism* or *racial discrimination*, yielding a ratio of 500 to 1.

Reason 2. Biological measures are redundant with questionnaire data

(Glei et al., PLOS ONE, 2016)

Reason 3. Biological plausibility is a hoax



Why do social scientists hate DNAm?

Reason 1. Biological measures distract from caring about social causes

Reason 2. Biological measures are redundant with questionnaire data

Reason 3. Biological plausibility is a hoax

Part 4: Why use it?

Reasons to study DNA methylation

1. Because it's there

2. Prediction of future disease

3. Biological pathway from the environment to disease

4. **As a <u>surrogate outcome</u> for wellbeing, disease and mortality**

GeroScience (2018) 40:419–436
https://doi.org/10.1007/s11357-018-0042-y

CrossMark

REVIEW ARTICLE

A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup

Jamie N. Justice · Luigi Ferrucci · Anne B. Newman · Vanita R. Aroda · Judy L. Bahnson · Jasmin Divers · Mark A. Espeland · Santica Marcovina · Michael N. Pollak · Stephen B. Kritchevsky · Nir Barzilai · George A. Kuchel

Received: 2 August 2018 / Accepted: 15 August 2018 / Published online: 27 August 2018

TAME: IL-6, TNFα-receptor I or II, CRP, GDF15, insulin, IGF1, cystatin C, NT-proBNP, and hemoglobin A1c. The present report provides a conceptual frame-

115TH CONGRESS
1ST SESSION

H. R. 4174

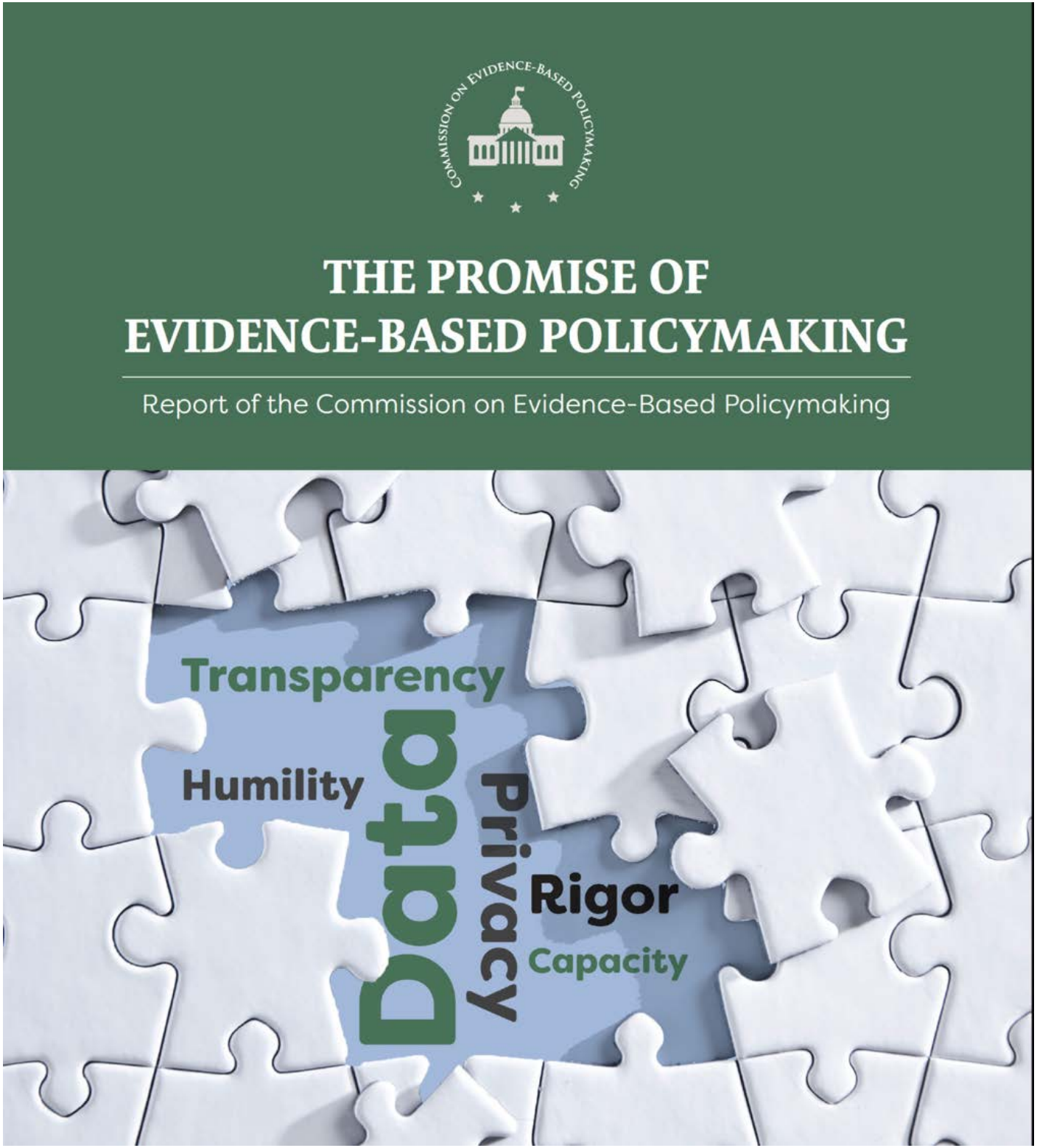
To amend titles 5 and 44, United States Code, to require Federal evaluation activities, improve Federal data management, and for other purposes.

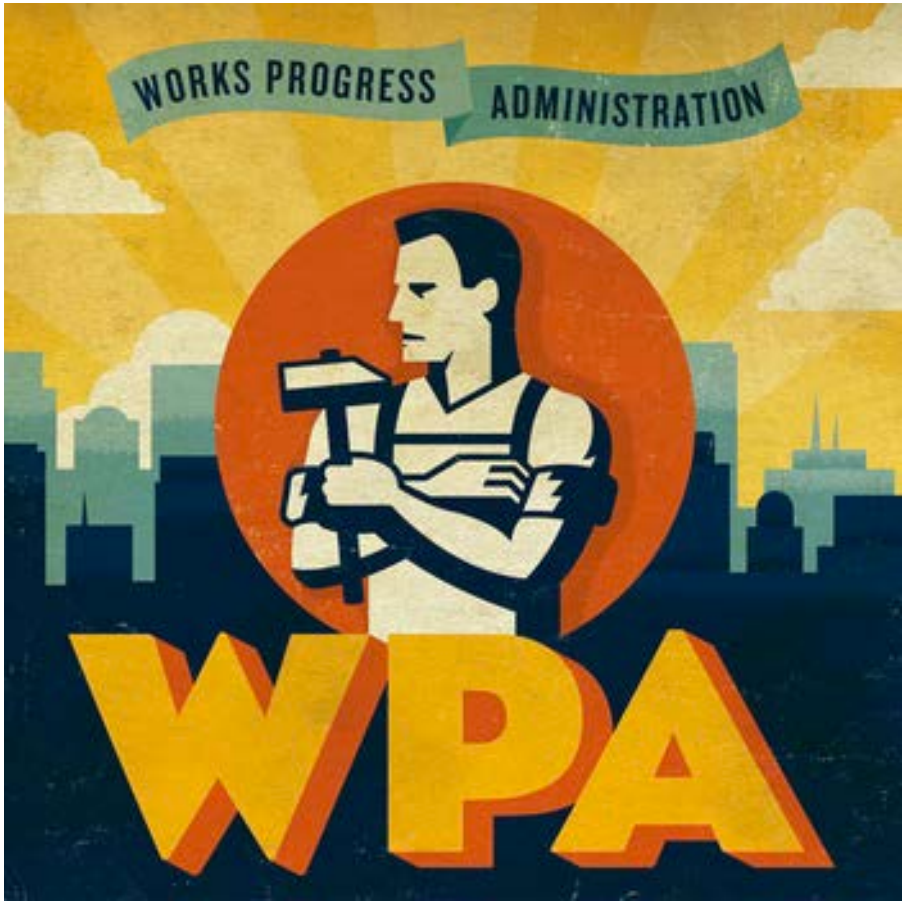
IN THE HOUSE OF REPRESENTATIVES

OCTOBER 31, 2017

Mr. RYAN of Wisconsin (for himself, Mr. FARENTHOLD, Mr. G
KILMER) introduced the following bill; which was referr
mittee on Oversight and Government Reform

"(4) EVIDENCE.—The term 'evidence' means evaluation, policy research and analysis, and information produced as a result of statistical activities conducted for a statistical purpose.


COMMISSION ON EVIDENCE-BASED POLICYMAKING
THE PROMISE OF EVIDENCE-BASED POLICYMAKING
Report of the Commission on Evidence-Based Policymaking
Transparency
Humility
Data
Privacy
Rigor
Capacity



Total expenditures were around $13.4 billion. At WPA's peak, it employed about three million people.

Between 1935 and 1943 WPA provided income for eight and a half million individuals.

OPPORTUNITY INSIGHTS

The Surrogate Index

A Tool to Facilitate Early Detection of Policies' Long-Term Impacts

Susan Athey (Stanford), Raj Chetty (Harvard), Guido Imbens (Stanford), and Hyunseung Kang (UW-Madison)

The impacts of many policies are observed with long delays. For example, it can take decades to see the effects of early childhood interventions on lifetime earnings or long-term health outcomes. This problem has greatly limited researchers' and policymakers' ability to test and improve policies.

difficult for social scientists to make use of statistical surrogates.

We develop a new method to combine multiple short-term indicators into a single "surrogate index" and show that this index can predict long-term outcomes, even when any single short-term indicator fails to do so. We

Technology of what we can measure

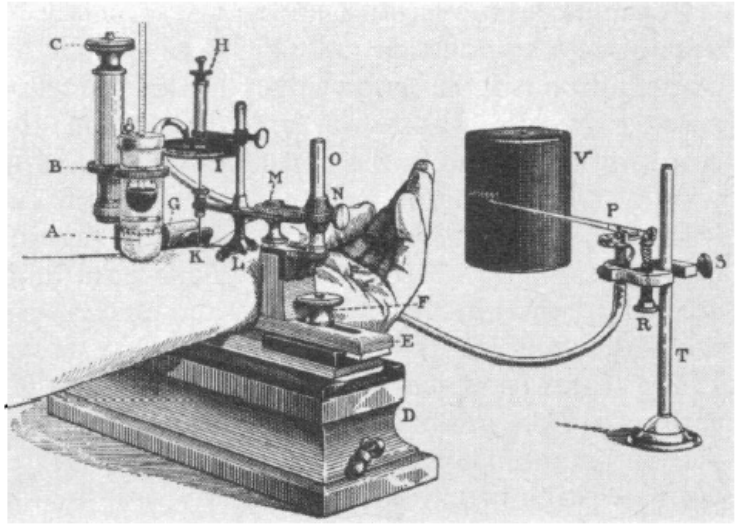
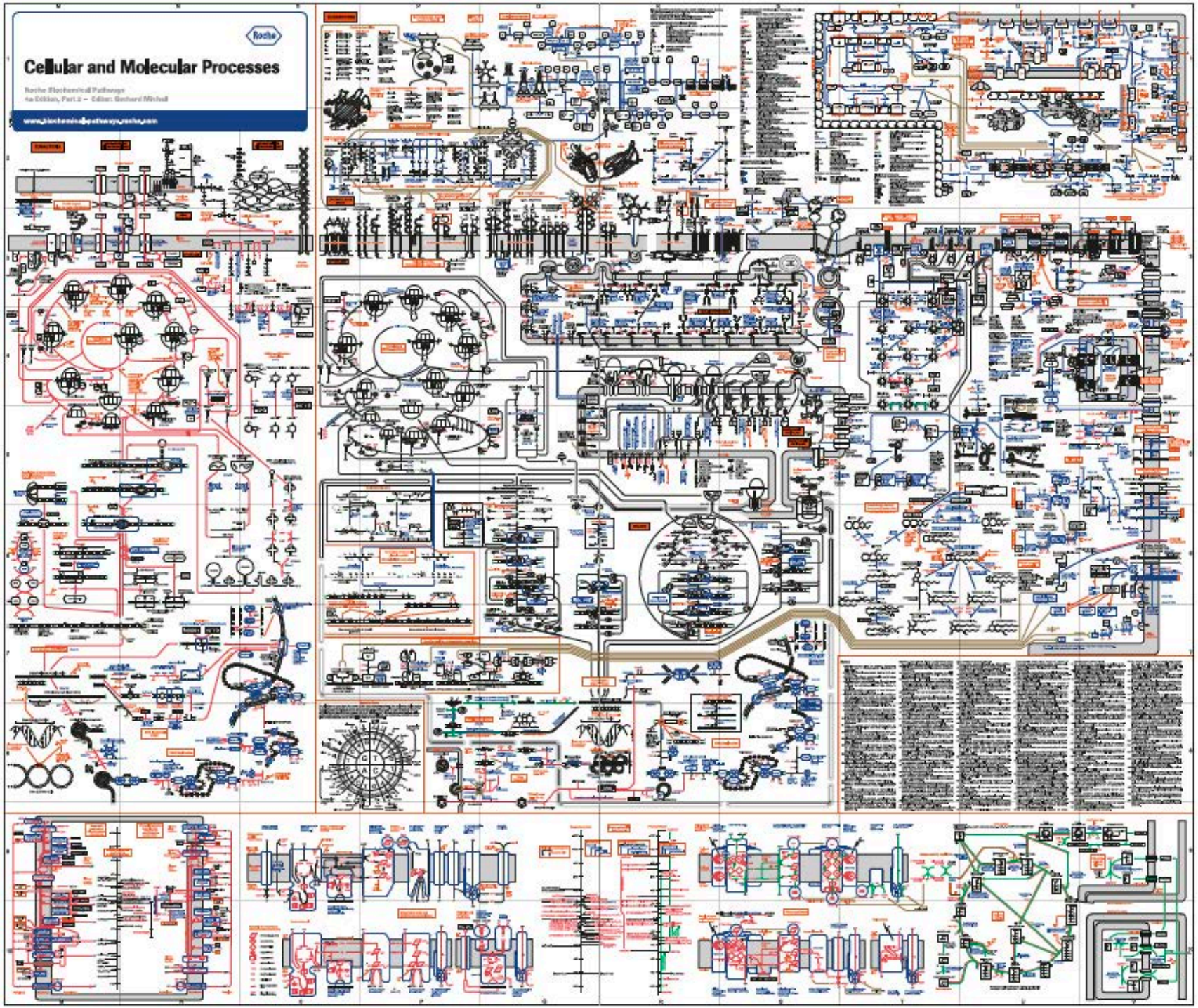
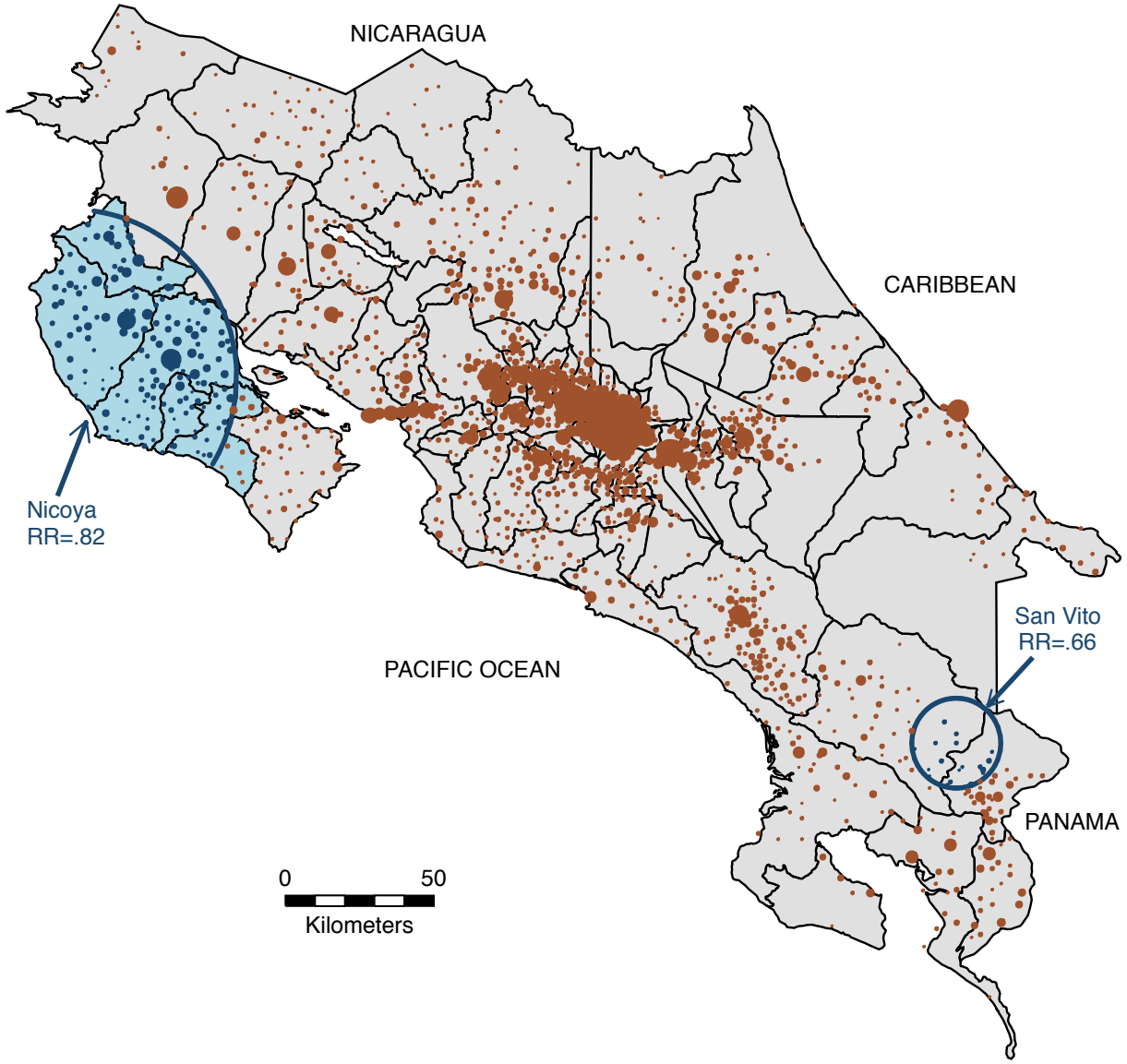


Fig 6 *Von Basch's sphygmomanometer and stand, invented about 1881. Despite its unwieldy appearance this is a simple device. The india rubber cap, A, rests on the radial artery and the arm is clamped between E and G. K is a fine pad which also rests against the artery. H is a fine screw by which the tambour of the sphygmograph can be adjusted and P is one of Marey's tambours which communicates by a piece of elastic tubing with the tambour of the sphygmograph (by courtesy of the Wellcome Trustees)*


Roche
Cellular and Molecular Processes
Roche Biochemical Pathways
4th Edition, Part 2 – Editor: Gerhard Michal

Two “islands” of low mortality



NOTES: Each point is a voting location. Points are proportional to population size. Canton limits shown.

POPULATION HEALTH METRICS

RESEARCH Open Access

Predicting mortality with biomarkers: a population-based prospective cohort study for elderly Costa Ricans

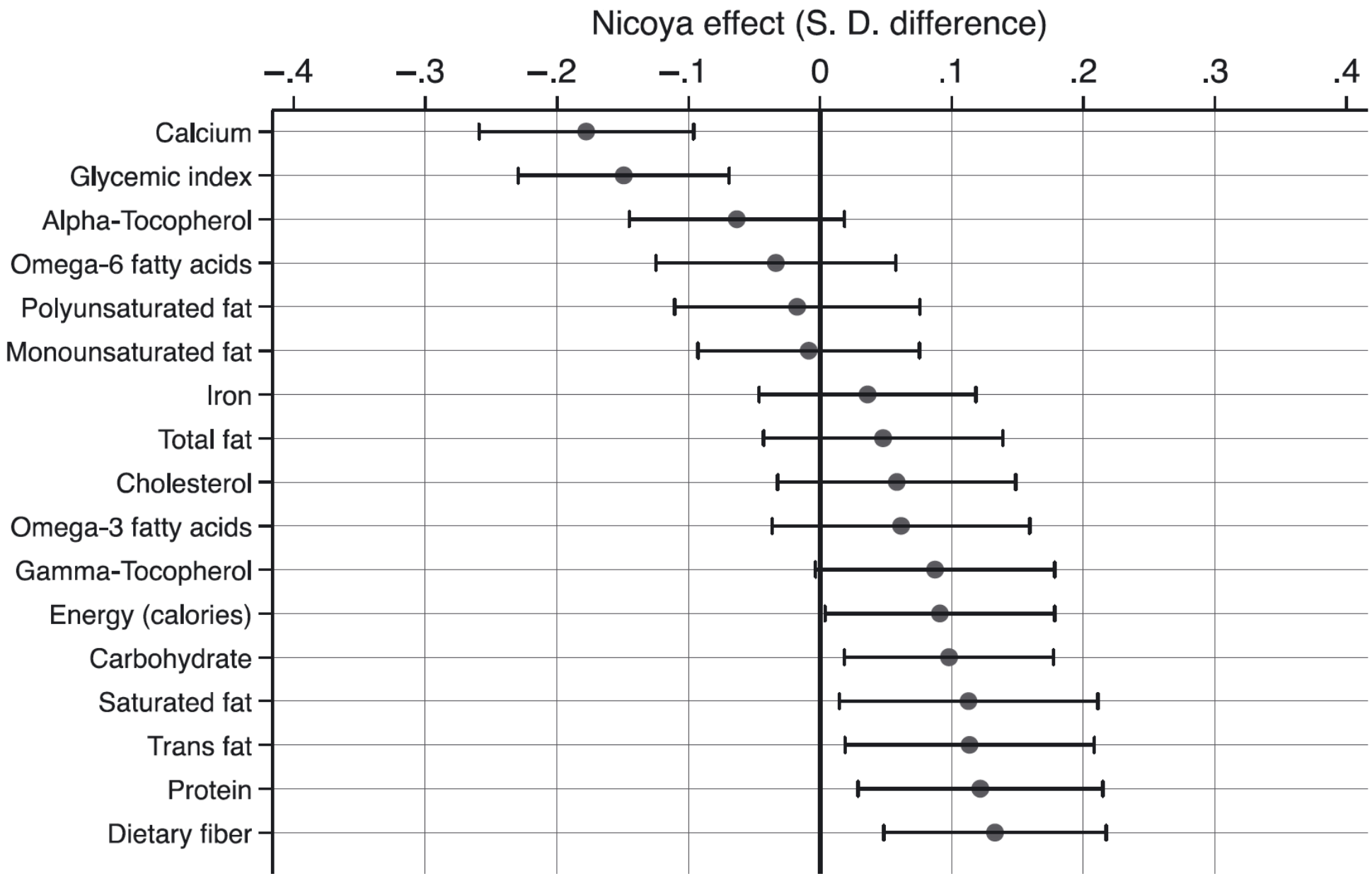
Luis Rosero-Bixby[1] and William H Dow[2*]

Table 1 Descriptive statistics of the 22 biomarkers investigated in the study

Biomarker	Units	Mean	SD	Proportion ≤1SD	Proportion < mean	Proportion ≥ 1SD	N
Metabolic hormones							
Glycosylated hemoglobin (HbA1c)	percent	5.76	1.13	0.01	0.69	0.09	2704
Fasting glucose	mg/dl	110.64	45.39	0.01	0.70	0.09	2748
CV biomarkers							
Diastolic blood pressure	mmHg	83.66	12.10	0.15	0.52	0.15	2883
Systolic blood pressure	mmHg	144.00	23.18	0.14	0.55	0.15	2883
Metabolic – lipids							
Triglycerides	mg/dl	162.84	85.27	0.10	0.62	0.13	2739
Total cholesterol	mg/dl	215.54	49.42	0.14	0.54	0.15	2746
HDL cholesterol	mg/dl	44.24	13.12	0.14	0.56	0.14	2743
Total/HDL cholesterol ratio	ratio	5.18	1.60	0.15	0.53	0.14	2743
LDL cholesterol	mg/dl	138.48	40.73	0.15	0.54	0.15	2581
Stress hormones							
Urinary cortisol	μg/g	26.22	24.99	0.00	0.66	0.09	2249
DHEAS	μg/dl	54.06	41.72	0.10	0.62	0.15	2706
Epinephrine	μg/g	7.41	10.95	0.00	0.69	0.07	1581
Norepinephrine	μg/g	37.63	32.21	0.01	0.65	0.09	1631
Inflammation, immune system							
CRP	mg/l	5.61	6.69	0.00	0.73	0.08	2677
Organ-specific functional reserve							
Creatinine clearance	mg/min	74.74	30.16	0.14	0.54	0.14	2401
Handgrip strength	kg	26.89	9.08	0.15	0.54	0.18	2595
Distance in 10 seconds	meters	5.51	2.52	0.13	0.46	0.12	2794
Pulmonary peak flow	l/min	304.66	118.65	0.15	0.57	0.17	2635
Nutrition, body size							
Knee height	cm	49.41	3.35	0.15	0.52	0.16	2788
Waist circumference	cm	93.88	12.37	0.15	0.51	0.14	2699
BMI	kg/m2	26.87	5.25	0.12	0.50	0.12	2789
Waist/hip ratio	ratio	0.948	0.077	0.14	0.49	0.13	2626

The following outlier observations were dropped: triglycerides: 6 observations >700 mg/dl; LDL-C: 4 obs. >300 mg/dl; cortisol: 7 obs. >400 μg/g; DHEAS: 4 obs. >300 μg/g; epinephrine: 2 obs. >150 μg/g; norepinephrine: 2 obs. >600 μg/g; CRP: 4 obs. >80 mg/l; creatinine: 3 obs. >250 mg/min; and waist circumference: 5 obs < 55 cm.
Statistics computed using sampling weights.

Taiwan [27], and the MacArthur, NHANES, and HRS studies carried out in the US [4,12,25], elderly Costa Ricans are found to be the worse off in most of their biomarkers, a paradoxical result given the higher life expectancy of adult Costa Ricans. For example, the mean systolic BP was 144 mmHg in Costa Rica, compared with 138 in the US and Taiwan. The prevalence of hypercholesterolemia (>250 mg/dL) in Costa Rica (30% of women and 15% of men) was more than double of that observed in Taiwan and the US [4]. The only biomarkers with healthier levels in Costa Rica were blood sugar, body mass index, and norepinephrine when compared with the US and blood sugar when compared with Taiwan.


Nicoya effect (S. D. difference)
−.4
−.3
−.2
−.1
0
.1
.2
.3
.4
Calcium
Glycemic index
Alpha-Tocopherol
Omega-6 fatty acids
Polyunsaturated fat
Monounsaturated fat
Iron
Total fat
Cholesterol
Omega-3 fatty acids
Gamma-Tocopherol
Energy (calories)
Carbohydrate
Saturated fat
Trans fat
Protein
Dietary fiber

Health factors	Nicoya	Other Costa Rica	Odds ratio	(95% CI)
Smoker currently	0.36	0.36	0.99	(0.94–1.05)
Smoker past	0.21	0.21	0.99	(0.83–1.18)
Physically active	0.30	0.27	1.18	(0.94–1.48)
Visited at home by health worker	0.45	0.41	1.15	(0.97–1.38)
Received flu vaccine	0.64	0.59	1.24 *	(1.04–1.49)
High BP medicine	0.46	0.51	0.82 +	(0.66–1.02)
Lipid lowering medicine	0.14	0.27	0.43 **	(0.32–0.59)
Diabetes medicine	0.18	0.20	0.87	(0.62–1.21)
Conditional on being sick:				
High BP medicine	0.63	0.67	0.86	(0.68–1.09)
Lipid lowering medicine	0.29	0.36	0.71 +	(0.48–1.04)
Diabetes medicine	0.53	0.55	0.92	(0.62–1.36)

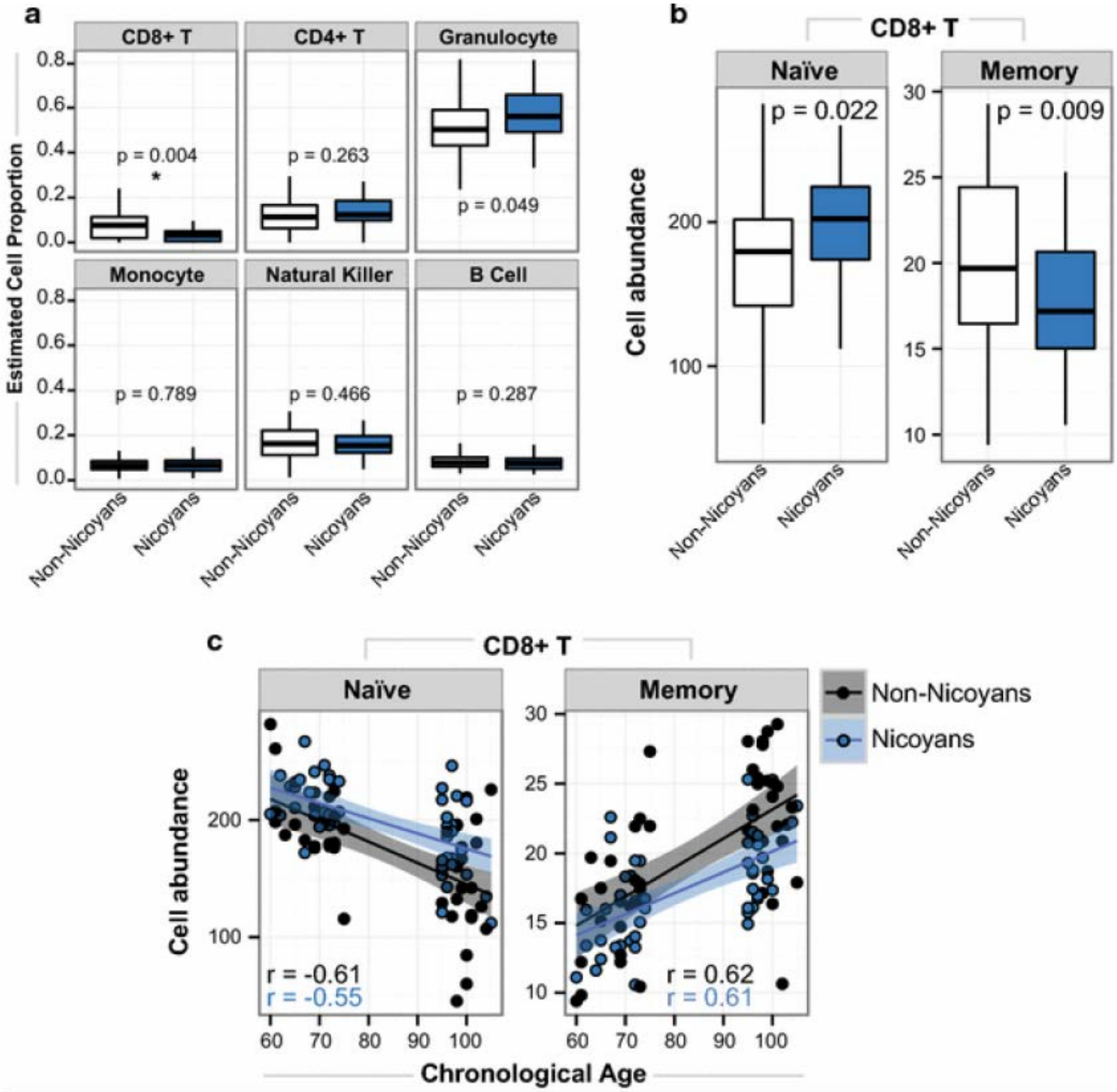
McEwen *et al. Epigenetics & Chromatin (2017) 10:21*
DOI 10.1186/s13072-017-0128-2

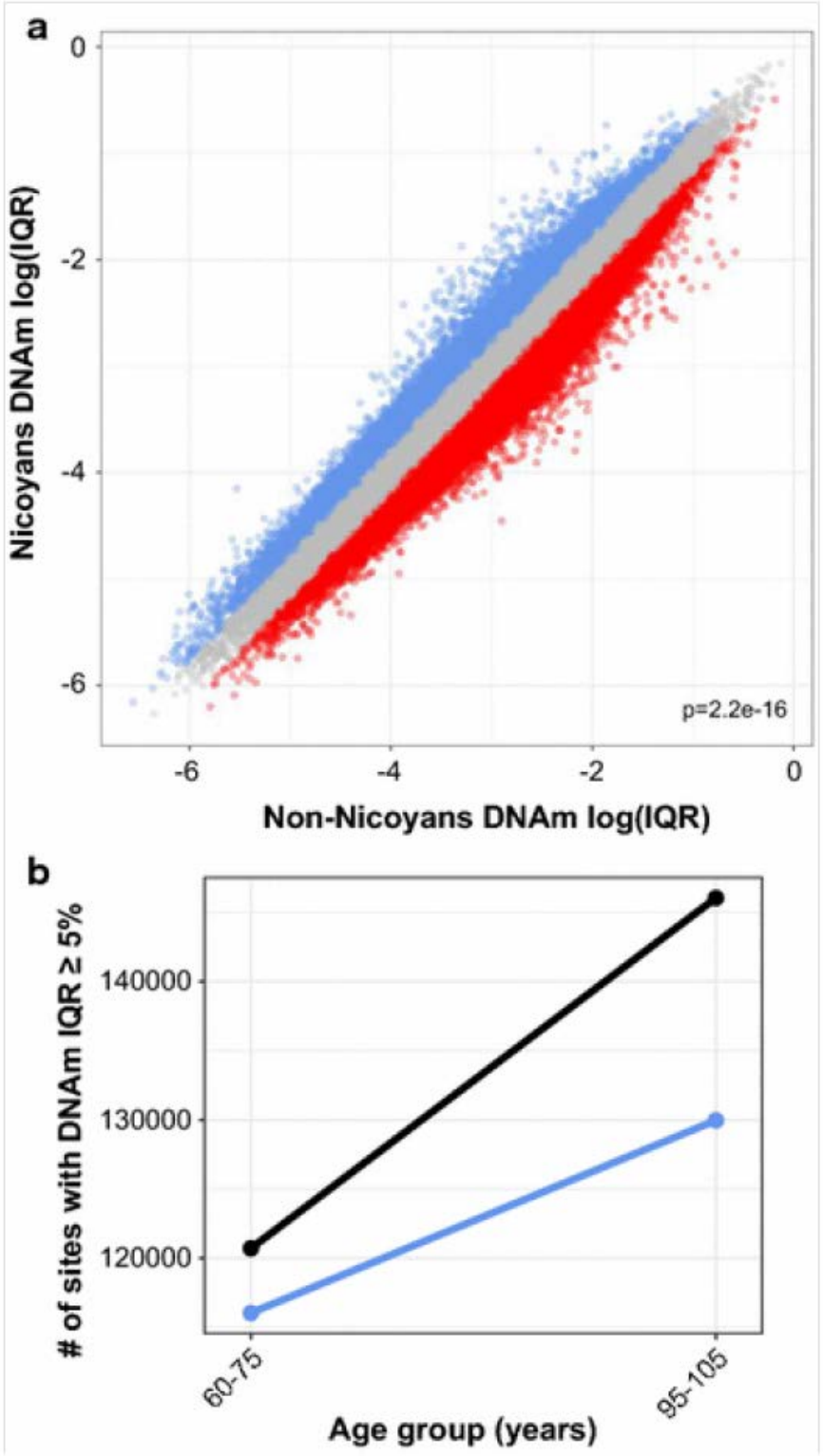
Epigenetics & Chromatin

RESEARCH Open Access

Differential DNA methylation and lymphocyte proportions in a Costa Rican high longevity region

Lisa M. McEwen[1], Alexander M. Morin[1], Rachel D. Edgar[1], Julia L. MacIsaac[1], Meaghan J. Jones[1], William H. Dow[2], Luis Rosero-Bixby[3], Michael S. Kobor[1] and David H. Rehkopf[4*]


a
CD8+ T
CD4+ T
Granulocyte
Monocyte
Natural Killer
B Cell
Estimated Cell Proportion
p = 0.004
*
p = 0.263
p = 0.049
p = 0.789
p = 0.466
p = 0.287
Non-Nicoyans
Nicoyans
b
CD8+ T
Naïve
Memory
Cell abundance
p = 0.022
p = 0.009
c
CD8+ T
Naïve
Memory
Non-Nicoyans
Nicoyans
Cell abundance
r = -0.61
r = -0.55
r = 0.62
r = 0.61
Chronological Age


a
Nicoyans DNAm log(IQR)
0
-2
-4
-6
p=2.2e-16
-6
-4
-2
0
Non-Nicoyans DNAm log(IQR)
b
# of sites with DNAm IQR ≥ 5%
140000
130000
120000
60-75
95-105
Age group (years)

Comprehensive outcomes for policy

American Journal of Epidemiology

DOI: 10.1093/aje/kwu277

Original Contribution

Systematic Assessment of the Correlations of Household Income With Infectious, Biochemical, Physiological, and Environmental Factors in the United States, 1999–2006

Chirag J. Patel, John P. A. Ioannidis, Mark R. Cullen, and David H. Rehkopf*

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Infectious, biochemical, physiological, and environmental factor measures

We assessed 330 infectious, biochemical, physiological, and environmental factors (Web Table 1). We described the type of factors by category; however, we modeled each factor separately in analyses.

We assessed indicators of 31 infectious agents, 24 of which were bacterial and 7 of which were viral. Results for 26 of these assays were either positive or negative, and those for the other 5 were continuous (as indicated in Web Table 1). The 90 biochemical and physiological factors included 19 body measures, 2 blood pressure measures, 2 pulse/heart rate measures, 20 blood cell parameters, and 47 serum- or urine-based biochemical measures. This last group included indicators of metabolic or cardiovascular-related phenotypes ($n = 12$), liver function ($n = 6$), kidney function ($n = 6$), iron levels ($n = 6$), bone health ($n = 2$), acid/base status of blood ($n = 5$), prostate health ($n = 3$), and hormone levels ($n = 2$) (see Web Table 1 for all factors).

The remaining factors included 209 environmental exposure markers, such as environmental chemicals and nutrients assayed from serum and urine. These included a serum marker of nicotine metabolism, 7 types of dioxins, 10 furans, 27 heavy metals, 21 hydrocarbons, 18 nutrients, 35 polychlorinated biphenyls, 24 pesticides, 13 phthalates, 6 phytoestrogens, and 25 volatile compounds.

Table 1. Overall Meta-Analytic Association Size for Validated Variables With Positive Correlations With Income, National Health and Nutrition Examination Survey, 1999–2006

Variable	Category	Association Size	Standard Error	*P* Value
α-Tocopherol	Nutrients	0.11	0.01	6.00E−41
trans-β-carotene	Nutrients	0.20	0.02	1.00E−40
Lutein/zeaxanthin	Nutrients	0.17	0.01	4.00E−33
cis-β-carotene	Nutrients	0.18	0.02	1.00E−32
Total mercury	Heavy metals	0.17	0.02	4.00E−26
trans-lycopene	Nutrients	0.10	0.01	5.00E−26
β-Cryptoxanthin	Nutrients	0.16	0.02	2.00E−24
Serum folate	Nutrients	0.12	0.01	4.00E−23
Red blood cell folate	Nutrients	0.09	0.01	8.00E−19
α-Carotene	Nutrients	0.20	0.02	2.00E−18
Perfluorooctanoic acid	Perfluorochemicals	0.14	0.02	4.00E−13
HDL-cholesterol	Biochemicals	0.11	0.02	5.00E−13
Perfluorooctane sulfonic acid	Perfluorochemicals	0.13	0.02	9.00E−13
Urine mercury	Heavy metals	0.10	0.02	2.00E−10
Bone mineral density	Body measures	0.05	0.01	2.00E−09
Blood urea nitrogen	Biochemicals	0.07	0.01	3.00E−09
Perfluorononanoic acid	Perfluorochemicals	0.15	0.03	5.00E−09
Total bilirubin	Biochemicals	0.07	0.01	6.00E−09
Albumin	Biochemicals	0.05	0.01	1.00E−08
Upper leg length	Body measures	0.06	0.01	9.00E−08
Bicarbonate	Biochemicals	0.05	0.01	2.00E−07
Monocyte percent	Blood measures	0.05	0.01	2.00E−07
Perfluorohexane sulfonic acid	Perfluorochemicals	0.09	0.02	3.00E−06

Question

Does DNA methylation represent a *substantial* and *impactful* biological mechanism through which environmental conditions impact health inequalities?

This is a *mediation* question.

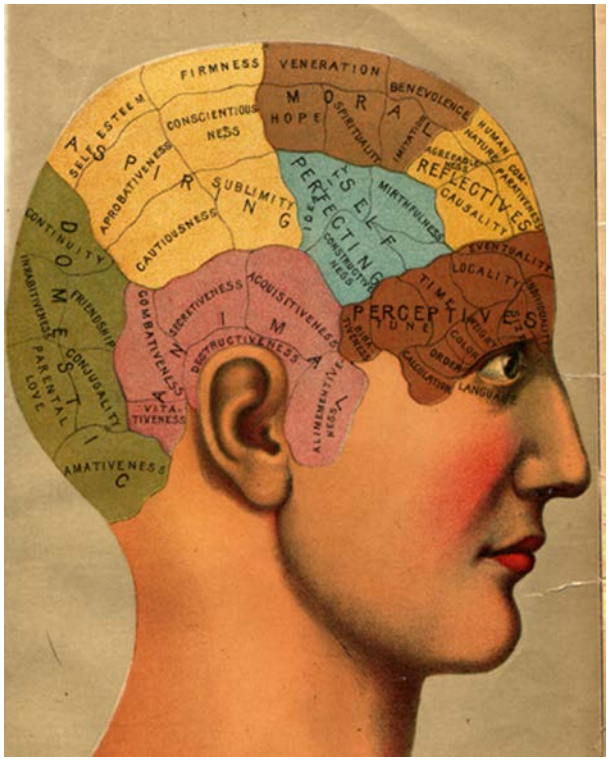
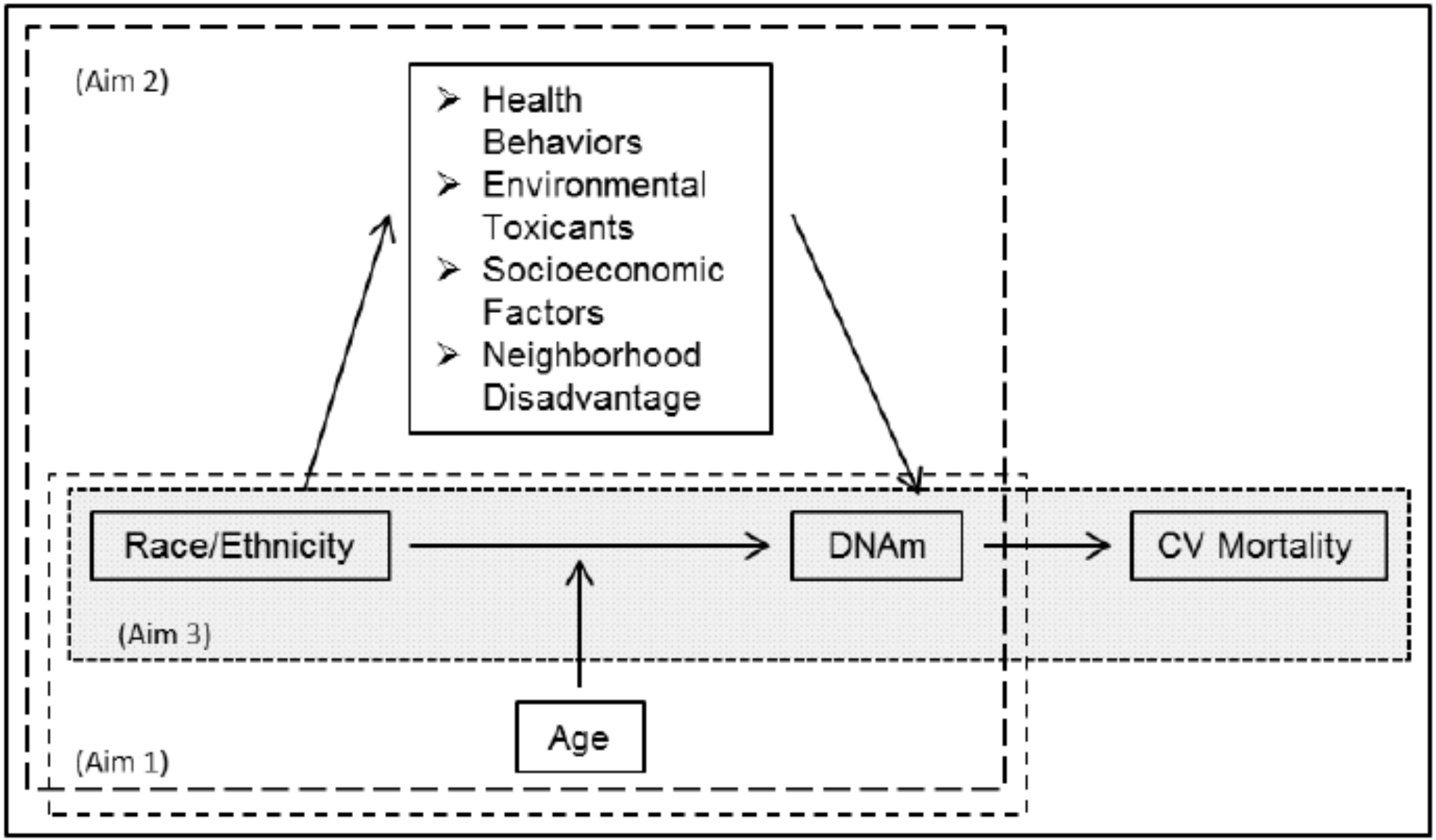


Figure 1. Conceptual Model of Racial/Ethnic Disparities in DNAm Patterns and Subsequent CV Mortality Risk



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Routledge
Taylor & Francis Group

Integrating Genetics and Social Science: Genetic Risk Scores

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The sequencing of the human genome and the advent of low-cost genome-wide assays that generate millions of observations of individual genomes in a matter of hours constitute a disruptive innovation for social science. Many public use social science datasets have or will soon add genome-wide genetic data. With these new data come technical

ARTICLE

DNA Methylation Analysis Identifies Loci for Blood Pressure Regulation

Melissa A. Richard,[1,52,*] Tianxiao Huan,[2,3,52] Symen Ligthart,[4,52] Rahul Gondalia,[5] Min A. Jhun,[6] Jennifer A. Brody,[7] Marguerite R. Irvin,[8] Riccardo Marioni,[9,10,11] Jincheng Shen,[12] Pei-Chien Tsai,[13] May E. Montasser,[14] Yucheng Jia,[15] Catriona Syme,[16] Elias L. Salfati,[17] Eric Boerwinkle,[18,19] Weihua Guan,[20] Thomas H. Mosley, Jr.,[21] Jan Bressler,[18] Alanna C. Morrison,[18] Chunyu Liu,[2,3,22] Michael M. Mendelson,[2,3,23] André G. Uitterlinden,[24] Joyce B. van Meurs,[24] BIOS Consortium, Oscar H. Franco,[4] Guosheng Zhang,[25,26,27] Yun Li,[25,28] James D. Stewart,[5,29] Joshua C. Bis,[7] Bruce M. Psaty,[30] Yii-Der Ida Chen,[15] Sharon L.R. Kardia,[6] Wei Zhao,[6] Stephen T. Turner,[31]

(Author list continued on next page)

Genome-wide association studies have identified hundred
tion accounts for a small fraction of the phenotypic varian

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DOI 10.1186/s13148-016-0304-4

Clinical Epigenetics

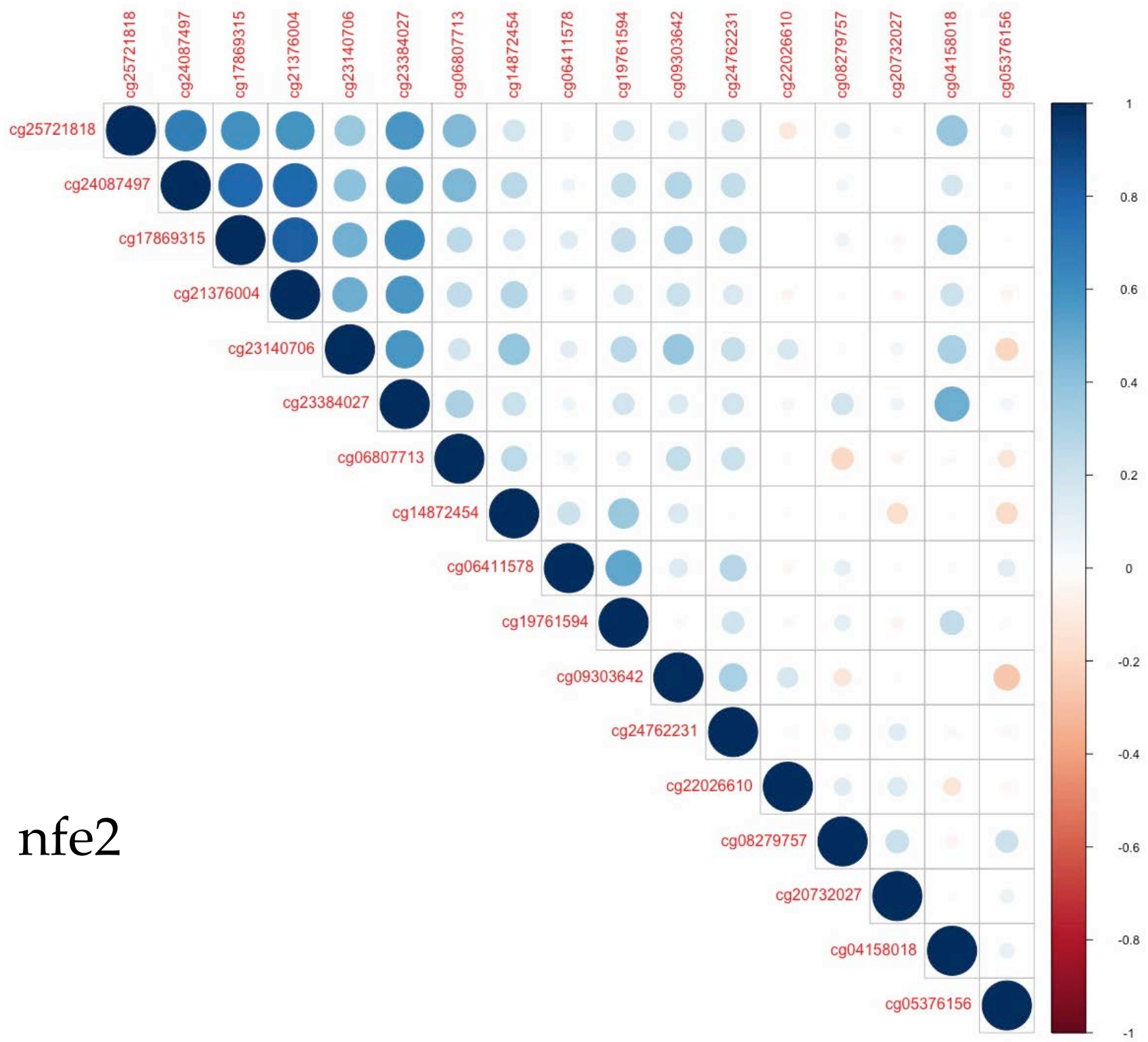
RESEARCH Open Access

Epigenome-wide association study (EWAS) on lipids: the Rotterdam Study

Kim V. E. Braun[1], Klodian Dhana[1], Paul S. de Vries[1,2], Trudy Voortman[1], Joyce B. J. van Meurs[3,4], Andre G. Uitterlinden[1,3,4], BIOS consortium, Albert Hofman[1,5], Frank B. Hu[5,6], Oscar H. Franco[1] and Abbas Dehghan[1*]

Abstract

Background: DNA methylation is a key epigenetic mechanism that is suggested to be associated with blood lipid levels. We aimed to identify CpG sites at which DNA methylation levels are associated with blood levels of triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol in 725 participants of the Rotterdam Study, a population-based cohort study. Subsequently, we sought replication in a non-overlapping set of 760 participants.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cg24762231
cg22026610
cg08279757
cg20732027
cg04158018
cg05376156
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0
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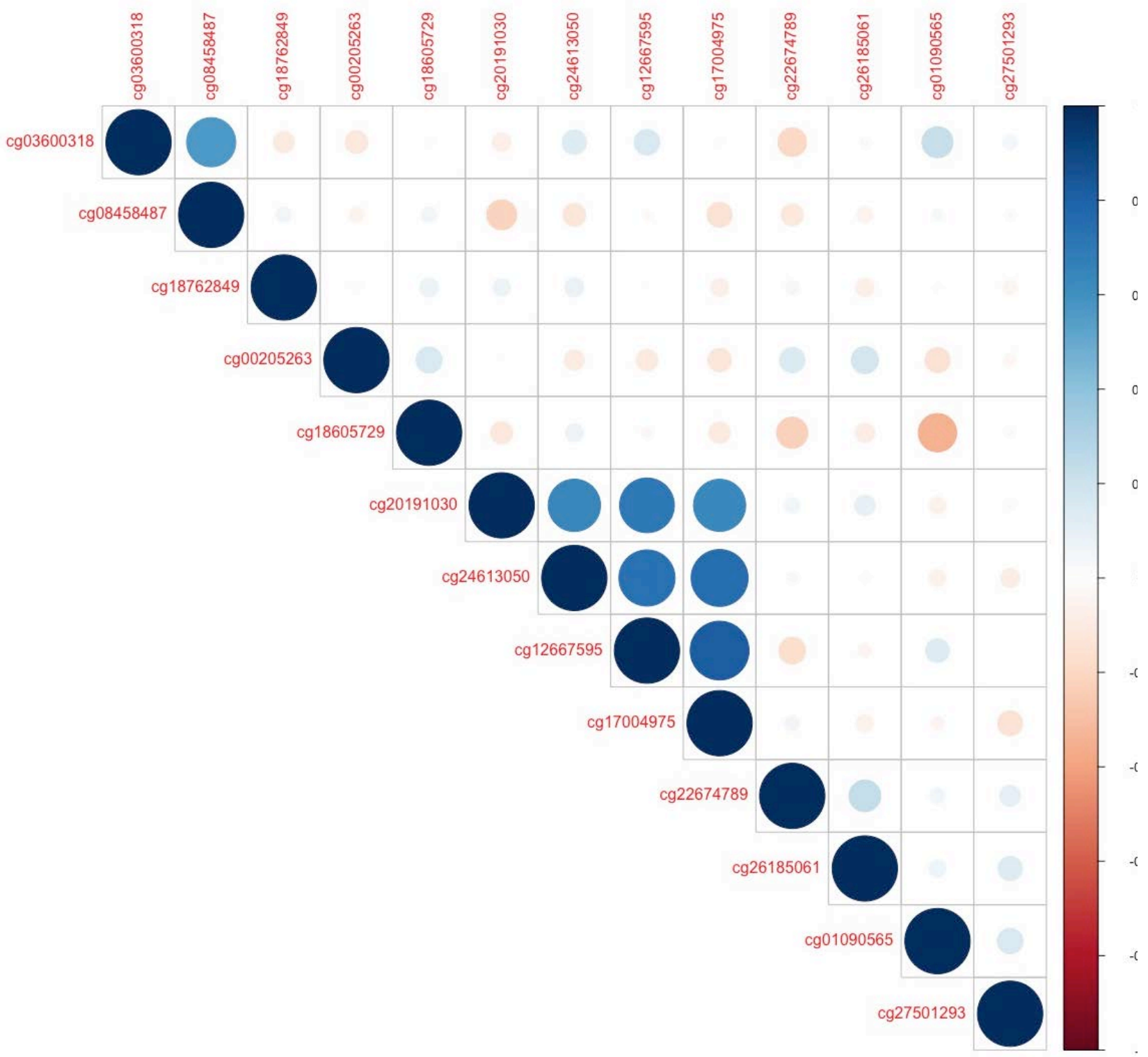
-0.4
-0.6
-0.8
-1

nfe2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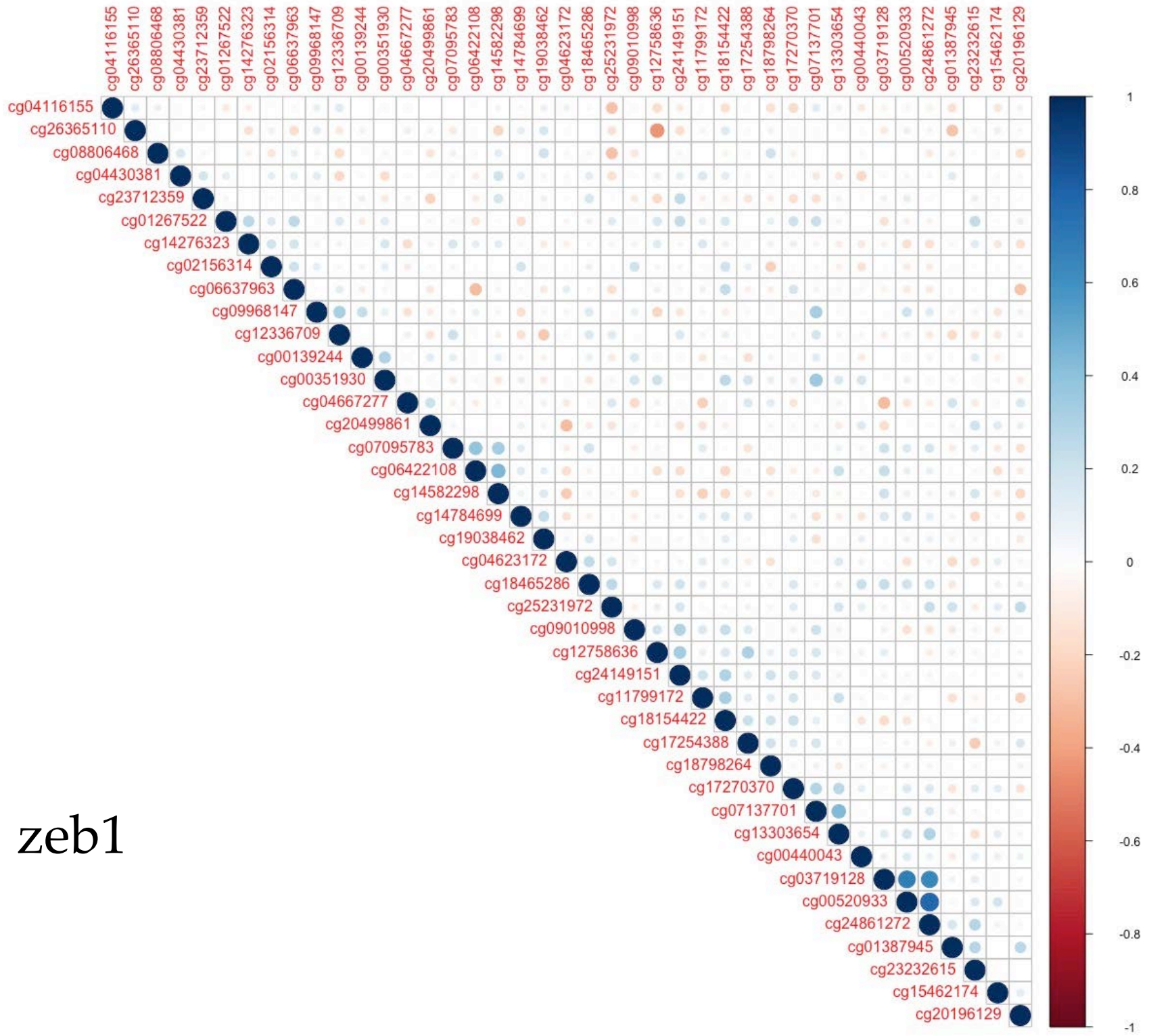
sftpd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1
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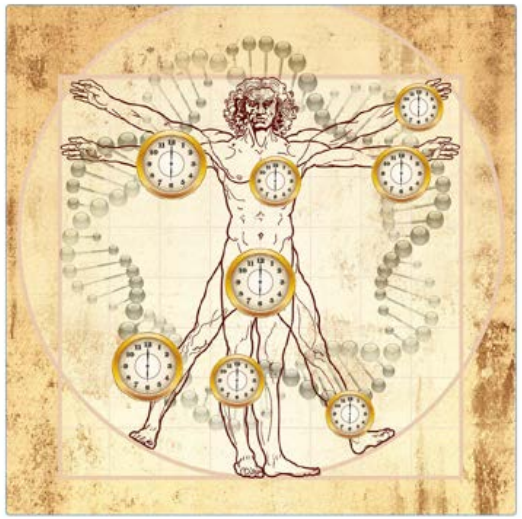
-0.6
-0.8
-1

zeb1

Genome Biology



DNA methylation age of human tissues and cell types

Horvath

BioMed Central

Horvath Genome Biology 2013, 14:R115
http://genomebiology.com/14/10/R115

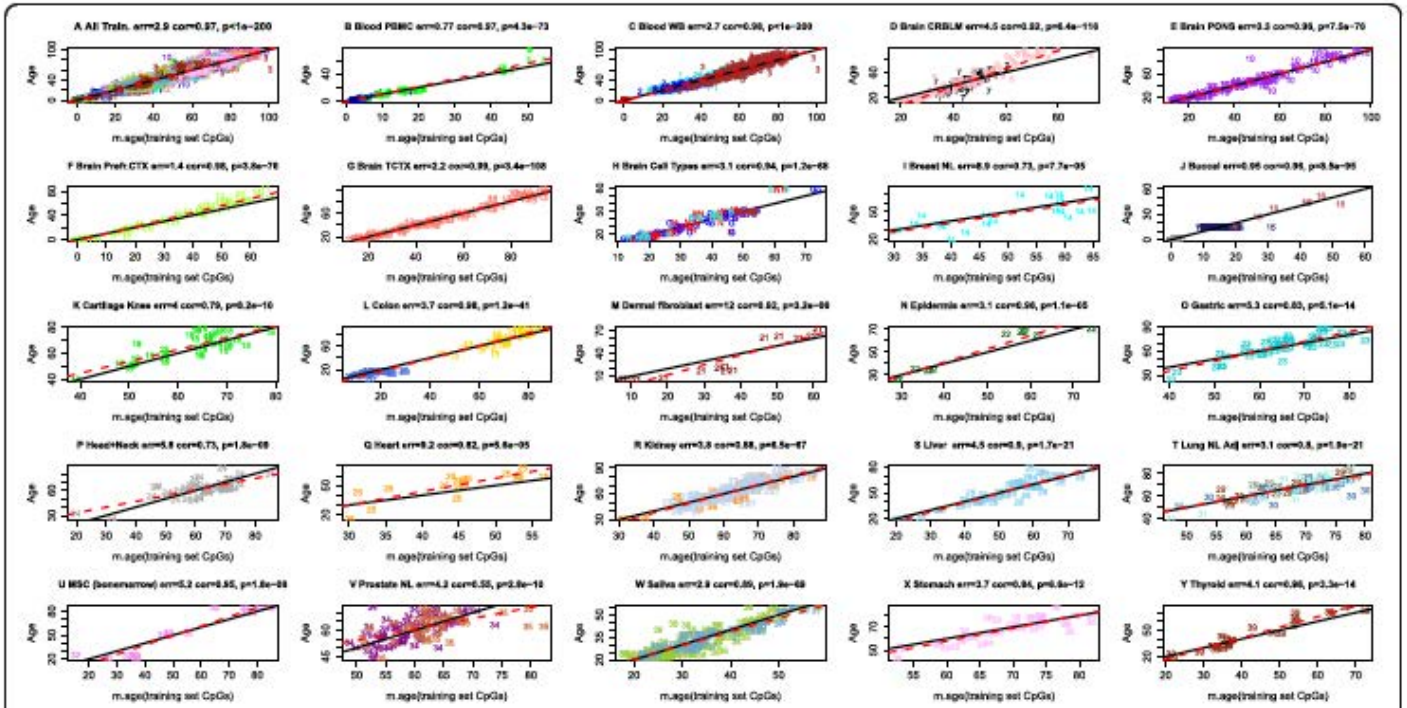


Figure 1 Chronological age (y-axis) versus DNAm age (x-axis) in the training data. Each point corresponds to a DNA methylation sample (human subject). Points are colored and labeled according to the underlying data set as described in Additional file 1. **(A)** Across all training data, the correlation between DNAm age (x-axis) and chronological age (y-axis) is 0.97 and the error (median absolute difference) is 2.9 years. Results for **(B)** peripheral blood mononuclear cells (cor = 0.97, error <1 year), **(C)** whole blood (cor = 0.98, error = 2.7 years), **(D)** cerebellum (cor = 0.92, error = 4.5), **(E)** pons (cor = 0.96, error = 3.3), **(F)** pre-frontal cortex (cor = 0.98, 1.4), **(G)** temporal cortex (cor = 0.99, error = 2.2), **(H)** brain samples, composed of 58 glial cell, 58 neuron cell, 20 bulk, and 9 mixed samples (cor = 0.94, error = 3.1), **(I)** normal breast tissue (cor = 0.73, error = 8.9), **(J)** buccal cells (cor = 0.95, error <1 year), **(K)** cartilage (cor = 0.79, error = 4), **(L)** colon (cor = 0.98, error = 3.7), **(M)** dermal fibroblasts (cor = 0.92, error = 12), **(N)** epidermis (cor = 0.96, error = 3.1), **(O)** gastric tissue (cor = 0.83, error = 5.3), **(P)** normal adjacent tissue from head/neck cancers (cor = 0.73, error = 5.8), **(Q)** heart (cor = 0.82, error = 9.2), **(R)** kidney (cor = 0.88, error = 3.8), **(S)** liver (cor = 0.90, error = 4.5), **(T)** lung (cor = 0.80, error = 3.1), **(U)** mesenchymal stromal cells (cor = 0.95, error = 5.2), **(V)** prostate (cor = 0.55, error = 4.2), **(W)** saliva (cor = 0.89, error = 2.9), **(X)** stomach (cor = 0.84, error = 3.7), **(Y)** thyroid (cor = 0.96, error = 4.1).

Breitling *et al. Clinical Epigenetics* (2016) 8:21
DOI 10.1186/s13148-016-0186-5

Clinical Epigenetics

RESEARCH Open Access

Frailty is associated with the epigenetic clock but not with telomere length in a German cohort

Lutz Philipp Breitling[1*], Kai-Uwe Saum[1], Laura Perna[1], Ben Schöttker[1,3], Bernd Holleczek[2] and Hermann Brenner[1,3]

Genome Biology

Open Access

DNA methylation age of blood predicts all-cause mortality in later life

Sonia Shah[3,4†], Allan F McRae[3,4†], Brian H Chen[5,6†], Elena Colicino[7†], Sarah E Harris[1,2], lenders[9], Paul Redmond[10], Simon R Cox[1,10], Alison Pattie[10], Janie Corley[10], Lee Murphy[8], nt W Montgomery[9], Andrew P Feinberg[11,12], M Daniele Fallin[11,13], Michael L Multhaup[11], Joehanes[5,15,16], Joel Schwartz[7,17], Allan C Just[7], Kathryn L Lunetta[5,18], Joanne M Murabito[5,19], orvath[21,22†], Andrea A Baccarelli[7,17†], Daniel Levy[5,6†], Peter M Visscher[1,3,4†], J Deary[1,10*†]

Mental Health

The epigenetic clock is correlated with physical and cognitive fitness in the Lothian Birth Cohort 1936

Riccardo E Marioni,[1,2,3] Sonia Shah,[3,4] Allan F McRae,[3,4] Stuart J Ritchie,[1,5] Graciela Muniz-Terrera,[6] Sarah E Harris,[1,2]

Epigenetic Clock							
Reference	**Population**	**Age Range**	**Follow-Up (yr)**	**Sample Size**	**HR Mort**	**95% CI, Mort**	**Risk Disease or Function**
(Perna et al. 2016), Hannum	German case-cohort, ESTHER	50-75	Per 5 yr	1548	1.21	1.14, 1.29	Cancer, CVD
(Perna et al. 2016), Horvath					1.11	1.05, 1.18	
(Chen et al. 2016), EEAA	Meta-Analysis, 13 cohorts			13089	1.04	1.03, 1.05	
(Zhang et al. 2017c), DNAm score (10 CpG)	German case-cohort, ESTHER	50-75	14	954	2.16	1.1, 4.24	
(Quach et al. 2017), EEAA	WHI	50-82		4173			
	InCHIANTI	71 ± 16	--	402			
(Zhang et al. 2018), AgeAccel	Subset of population-based cohort	62.1 ± 6.5	14	858	1.37	1.25,1.51	
(Zhang et al. 2018), Methylation risk (MR) score	Subset of population-based cohort	62.9 ± 6.7	14	993	1.91	1.63, 2.22	
(Levine et al. 2018), PhenoAge	5 studies: women's health (WHI), Framingham Heart (FHS), Normative Aging (NAS), Jackson Heart (JHS)		10	WHI: 2191 FHS: 2553 NAS: 657 JHS: 1747	Meta: 1.045		Healthspan; CVD, cancer, AD, T2D, respiratory
(Starnawska et al. 2017), DNAm score	Middle-aged twins		10	486			NOT Cognitive function
(Marioni et al. 2015), Hannum	5 cohorts: Lothian Birth cohorts (1921, 1936), Framingham Heat (FHS), Normative Aging (NAS	~60-80	Per 5 yr	1921: 446 1936: 920 FHS: 2635 NAS 657	1.21	1.14, 1.29	
(Marioni et al. 2015), Horvath					1.11	1.05, 1.19	

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Research Paper

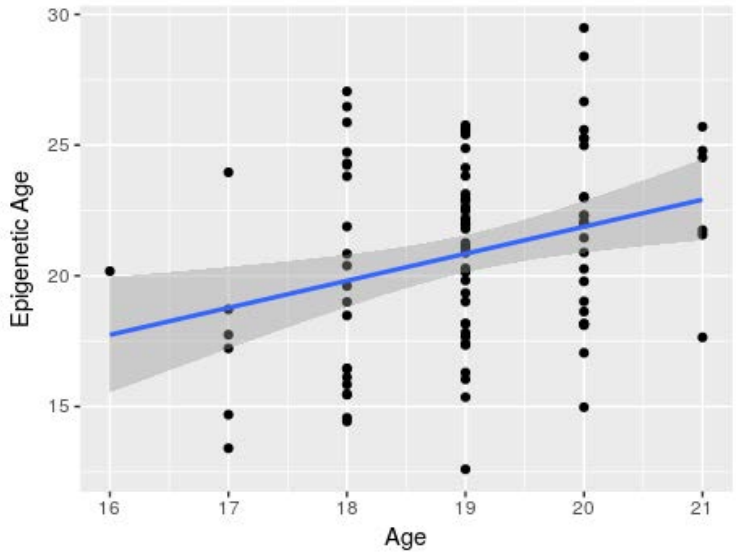
DNA methylation age of blood predicts future onset of lung cancer in the women's health initiative

Morgan E. Levine[1,2], H. Dean Hosgood[3], Brian Chen[4], Devin Absher[5,*], Themistocles Assimes[6,*], and Steve Horvath[1,7,*]

[1] *Human Genetics, David Geffen School of Medicine, University of California LA, Los Angeles, CA 90095, USA;*
[2] *Center for Neurobehavioral Genetics, University of California Los Angeles, Los Angeles, California 90095, USA;*
[3] *Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, USA;*
[4] *Longitudinal Study Section, Translational Gerontology Branch, Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA;*

Is there a difference in epigenetic age between average and overweight women?

$$\text{epigenetic age} \sim \beta_0 + \beta_1 * \text{age} + \varepsilon$$

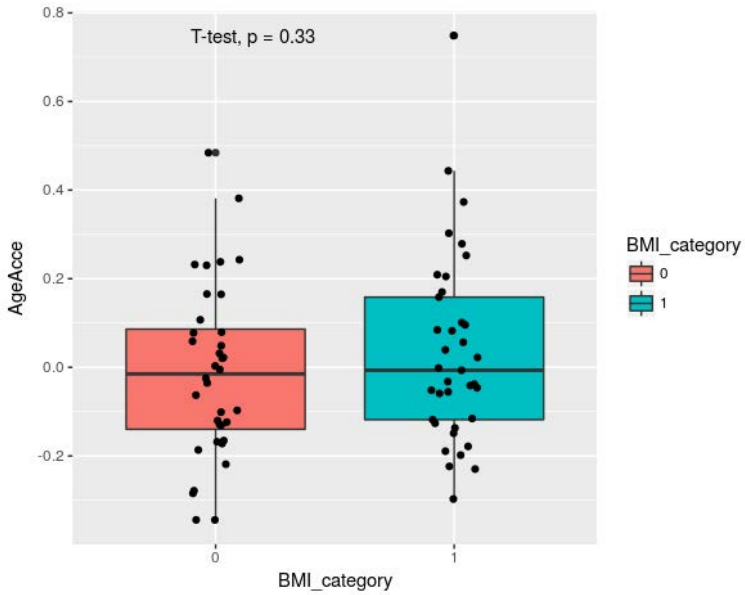


P-value 0.0068

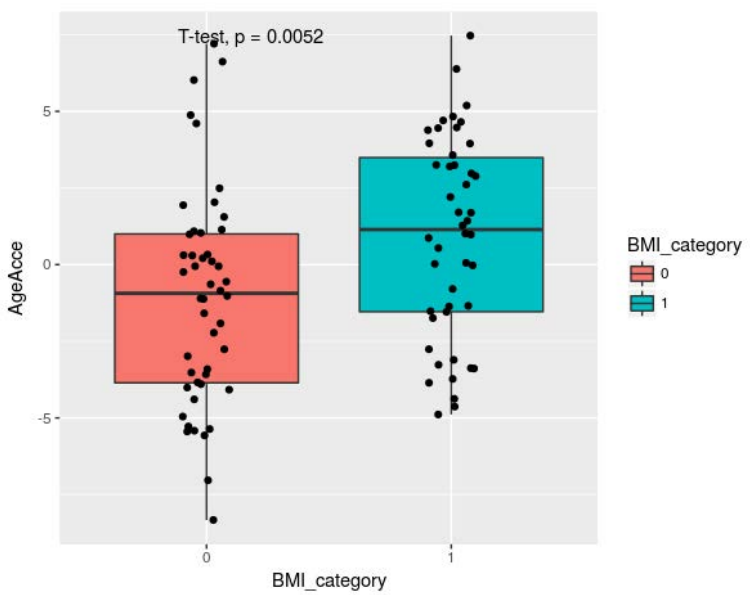
The residuals (age acceleration) is compared across groups.

Obesity accelerates epigenetic aging in human blood

Newborn



Adult



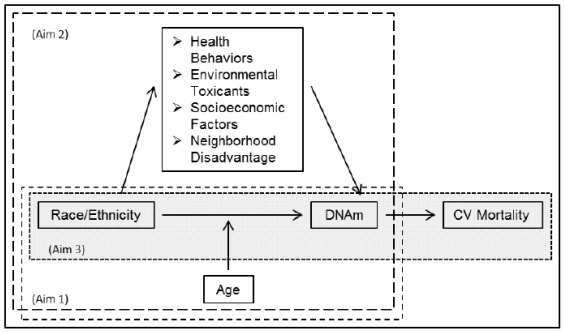
Specifics for making DNAm useful for health inequalities research

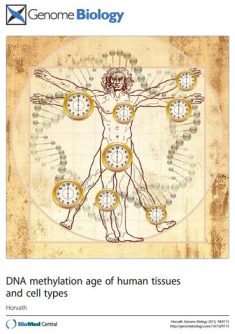
1. For policy relevance, utilize as, and within, a constellation of surrogate outcomes

2. Conduct mediation analysis

3. Use summary DNAm measures that are associated with wellbeing, health and disease

Figure 1. Conceptual Model of Racial/Ethnic Disparities in DNAm Patterns and Subsequent CV Mortality Risk





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Canadian Institutes of Health Research
NIH (R21 MD013296, R01 HD091262,
R01 MD011721)

Thank you.


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